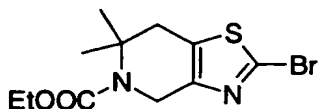


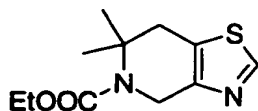
Ethyl 2-bromo-6,6-dimethyl-6,7-dihydrothiazolo[4,5-c]-pyridine-5(4H)-carboxylate:



¹H-NMR (CDCl₃) δ: 1.26(3H,t,J=7.1Hz), 1.55(6H,s), 2.79-2.81(2H,m), 4.10(2H,q,J=7.1Hz), 4.65-4.67(2H,m).

[Referential Example 314]

453

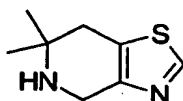


n-Butyllithium (1.56N hexane solution, 1.04 ml) was added to a solution with the compound (432 mg) obtained in Referential Example 313 in diethyl ether (5 ml) at -78°C, and the mixture was stirred at -78°C for 30 minutes. Water and diethyl ether were added to the reaction mixture to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off to obtain the title compound (307 mg).

¹H-NMR (CDCl₃) δ: 1.28(3H,t,J=7.1Hz), 1.55(6H,s), 2.90(2H,s), 4.12(2H,q,J=7.1Hz), 4.75(2H,m), 8.63(1H,s).

[Referential Example 315]

6,6-Dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine:



The compound (307 mg) obtained in Referential Example 314 was dissolved in a mixed solvent of water (5 ml), ethanol (5 ml) and dioxane (5 ml), and lithium hydroxide (598 mg) was added to this reaction mixture to heat the mixture under reflux for 7 days. After allowing the reaction mixture to cool to room temperature, water and methylene chloride were added to conduct liquid separation. The resultant water layer was extracted 6 times with methylene chloride. The resultant organic layers were

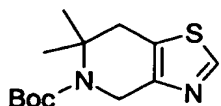
dried over anhydrous sodium sulfate, and the solvent was distilled off to obtain the title compound (207 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.23(6H,s), 2.71-2.73(2H,m), 4.09-4.11(2H,m), 8.61(1H,s).

5 MS (ESI) m/z : 168(M^+).

[Referential Example 316]

tert-Butyl 6,6-dimethyl-6,7-dihydrothiazolo[4,5-c]pyridine-5(4H)-carboxylate:



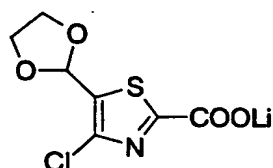
10 The compound (207 mg) obtained in Referential Example 315 was dissolved in methylene chloride (5 ml), and di-tert-butyl dicarbonate (404 mg) and 4-(N,N-dimethylamino)-pyridine (151 mg) were added to stir the mixture at room temperature for 2 hours. Di-tert-butyl dicarbonate (404
15 mg) was additionally added, and the mixture was stirred overnight at room temperature. Further, di-tert-butyl dicarbonate (1.00 g) was added, and the mixture was stirred for 1 hour. Methylene chloride and 10% hydrochloric acid were added to conduct liquid separation. The resultant
20 organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (95.4 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.47(9H,s), 1.52(6H,s), 2.87(2H,s),
25 4.69(2H,s), 8.62(1H,s).

MS (ESI) m/z: 269(M+H)⁺.

[Referential Example 317]

Lithium 4-chloro-5-(1,3-dioxolan-2-yl)thiazole-2-carboxylate:



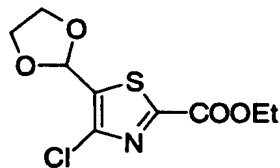
5

2,4-Dichlorothiazole-5-carbaldehyde ethyleneacetal (J. Chem. Soc. Perkin Trans. 1, 1992, p. 973) (2.26 g) was dissolved in tetrahydrofuran (15 ml), and n-butyllithium (1.5N hexane solution, 6.8 ml) was added under cooling with dry ice-acetone to stir the mixture for 20 minutes. At the same temperature, carbon dioxide was then introduced. The reaction mixture was gradually heated to room temperature over 1.5 hours and then concentrated. Hexane was added to the reaction mixture to powder the product. The product was collected by filtration and suspended in ethyl acetate, and formed powder was collected again by filtration to obtain the title compound (1.65 g).

15

[Referential Example 318]

Ethyl 4-chloro-5-(1,3-dioxolan-2-yl)thiazole-2-carboxylate:



20

The compound (242 mg) obtained in Referential Example

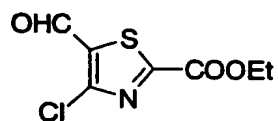
317 and ethanol (0.2 ml) were dissolved in N,N-dimethylformamide (2 ml), and 1-hydroxybenzotriazole monohydrate (136 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (250 mg) were added to stir
5 the mixture at room temperature for a night. The solvent was distilled off under reduced pressure, and diethyl ether and diluted hydrochloric acid were added to separate an organic layer. The organic layer was washed with water and a saturated aqueous solution of sodium hydrogencarbonate
10 and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (170 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.43(3H,t,J=7.3Hz), 4.00-4.10(2H,m), 4.10-4.20(2H,m), 4.48(2H,q,J=7.3Hz), 6.15(1H,s).

15 MS (ESI) m/z: 264(M+H) $^+$.

[Referential Example 319]

Ethyl 4-chloro-5-formylthiazole-2-carboxylate:



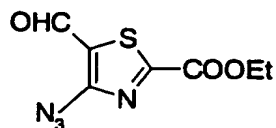
The compound (132 mg) obtained in Referential Example
20 318 was dissolved in diethyl ether (5 ml), and 20% hydrochloric acid (0.3 ml) was added to stir the mixture at room temperature for 7 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct extraction with diethyl ether. The
25 extract was dried over anhydrous magnesium sulfate, and the

solvent was distilled off under reduced pressure to obtain the title compound (110 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.46 (3H, t, $J=7.1\text{Hz}$), 4.52 (2H, q, $J=7.1\text{Hz}$), 10.12 (1H, s).

5 [Referential Example 320]

Ethyl 4-azido-5-formylthiazole-2-carboxylate:

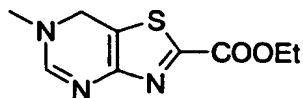


The compound (5.15 g) obtained in Referential Example 319 was dissolved in dimethyl sulfoxide (30 ml), and sodium
10 azide (1.52 g) was added to stir the mixture at room temperature for 2.5 hours. Ice water was added to the reaction mixture to conduct extraction with diethyl ether. The extract was washed twice with water and then dried over anhydrous magnesium sulfate. The solvent was distilled off
15 under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 24:1) to obtain the title compound (1.78 g)

$^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (3H, t, $J=7.1\text{Hz}$), 4.50 (2H, q, $J=7.1\text{Hz}$),
20 9.95 (1H, s).

[Referential Example 321]

Ethyl 6-methyl-6,7-dihydrothiazolo[4,5-d]pyrimidine-2-carboxylate:



The compound (1.56 g) obtained in Referential Example 320 was dissolved in methylene chloride (20 ml), and acetic acid (2 ml), methylamine (2N tetrahydrofuran solution, 21 ml) and sodium triacetoxymethylborohydride (2.98 g) were added to stir the mixture. After 1 hour, sodium triacetoxymethylborohydride (2.98 g) was additionally added, and the stirring was continued for additional 4.5 hours. A 0.5N aqueous solution (100 ml) of sodium hydroxide was added to the reaction mixture to alkalify it. After the reaction mixture was extracted with methylene chloride, the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain a brown oil (1.43 g). This oil was dissolved in ethanol (50 ml), 10% palladium on carbon (2.0 g) was added to conduct hydrogenation at normal temperature and pressure. After 2.5 hours, the catalyst was removed by filtration, and the filtrate was concentrated. The residue was dissolved in methylene chloride (30 ml), and trimethyl orthoformate (0.7 ml) and boron trifluoride-diethyl ether complex (0.3 ml) were added to stir the mixture at room temperature for 15 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct extraction with methylene chloride. The extract was dried over anhydrous sodium sulfate. The solvent was

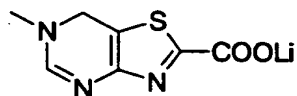
distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 97:3) to obtain the title compound (100 mg).

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (3H, t, $J=7.1\text{Hz}$), 2.95 (3H, s), 4.44 (2H, q, $J=7.1\text{Hz}$), 4.87 (2H, s), 7.06 (1H, s).

MS (ESI) m/z : 226 ($\text{M}+\text{H}$) $^+$.

[Referential Example 322]

Lithium 6-methyl-6,7-dihydrothiazolo[4,5-d]pyrimidine-2-
10 carboxylate:

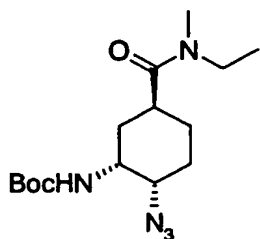


The compound (463 mg) was dissolved in tetrahydrofuran (20 ml), and lithium hydroxide (54.1 mg) and water (4 ml) were added to stir the mixture at room
15 temperature for 4.5 hours. The solvent was distilled off under reduced pressure, and the residue was dried by means of a vacuum pump to obtain the title compound (460 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.86 (3H, s), 4.71 (2H, s), 7.03 (1H, s).

[Referential Example 323]

20 tert-Butyl (1R,2S,5S)-2-azido-5-{[ethyl(methyl)amino]-carbonyl}cyclohexylcarbamate:



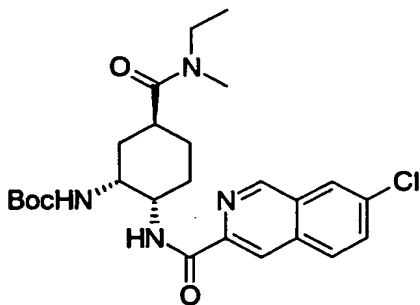
The title compound was obtained by condensing the compound obtained in Referential Example 250 with ethylmethylaniline.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.08, 1.18 (total 3H, each t, $J=7.1\text{Hz}$), 1.46 (9H, s), 1.52-1.80 (4H, m), 2.04-2.08 (2H, m), 2.71-2.77 (1H, m), 2.89, 2.98 (total 3H, each s), 3.32, 3.39 (total 2H, each q, $J=7.1\text{Hz}$), 3.74-3.76 (1H, m), 4.09-4.11 (1H, m), 4.60 (1H, br. s).

10 MS (EI) m/z : 326 ($M+H$) $^+$.

[Referential Example 324]

tert-Butyl (1R,2S,5S)-2-[[(7-chloroisoquinolin-3-yl)-carbonyl]amino]-5-[[ethyl(methyl)amino]carbonyl]-cyclohexylcarbamate:



15

The compound (1.44 g) obtained in Referential Example 323 was dissolved in methanol (20 ml), 10% palladium on carbon (150 mg) was added, and the mixture was stirred

under a hydrogen atmosphere. After 24 hours, the catalyst was removed by filtration, and the solvent was then concentrated under reduced pressure to obtain a colorless oil. This oil was used in the next reaction as it is.

5 The above-obtained oil was dissolved in methylene chloride (30 ml), and the compound (850 mg) obtained in Referential Example 57, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.27 g), 1-hydroxybenzotriazole monohydrate (900 mg) and N-methylmorpholine (1.34 g) were
10 added to stir the mixture at room temperature. After 17 hours, methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the reaction mixture to conduct liquid separation, and the resultant organic layer was dried over anhydrous magnesium sulfate.
15 The solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography on silica gel (methanol:methylene chloride = 1:50) to obtain the title compound (1.61 g).

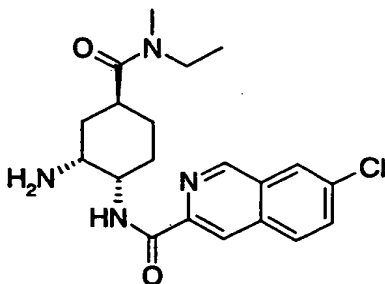
¹H-NMR (CDCl₃) δ: 1.10, 1.22 (total 3H, each t, J=7.1Hz),
20 1.43 (9H, s), 1.84-2.17 (6H, m), 2.66 (1H, br. s), 2.92, 3.03 (total 3H, each s), 3.35-3.44 (2H, m), 4.20-4.30 (2H, m), 5.30 (1H, br. s), 7.70 (1H, d, J=8.6Hz), 7.92 (1H, d, J=8.6Hz), 8.00 (1H, s), 8.40 (1H, br. s), 8.56 (1H, s), 9.03 (1H, s).

MS (FAB) m/z: 489 (M+H)⁺.

25 [Referential Example 325]

N-((1S,2R,4S)-2-Amino-4-[(7-chloroisoquinolin-3-yl)-carbonyl]-4-{[ethyl(methyl)amino]carbonyl}cyclohexyl)-7-

chloroisoquinoline-3-carboxamide:



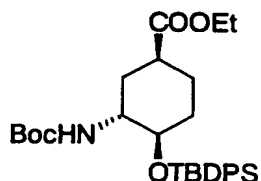
The compound (1.60 g) obtained in Referential Example 324 was dissolved in an ethanol solution (25 ml) of
5 hydrochloric acid, and the solution was stirred at room temperature for 30 minutes. The solvent was distilled off under reduced pressure, and methylene chloride and a 1N aqueous solution of sodium hydroxide were added to the residue to conduct liquid separation. The resultant water
10 layer was extracted with methylene chloride, and organic layers were combined and dried over potassium carbonate. The solvent was distilled off under reduced pressure, hexane was added to the residue, and precipitate was collected by filtration to obtain the title compound (1.22
15 g).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.10, 1.23 (total 3H, each t, $J=7.1\text{Hz}$),
1.26 (2H, br.s), 1.69–2.11 (6H, m), 2.89 (1H, br.s),
2.93, 3.05 (total 3H, each s), 3.38–3.45 (2H, m), 3.52 (1H, s),
4.18 (1H, br.s), 7.70 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.94 (1H, d, $J=8.8\text{Hz}$),
20 8.02 (1H, d, $J=2.0\text{Hz}$), 8.50 (1H, br.s), 8.59 (1H, s), 9.11 (1H, s).

MS (FAB) m/z : 389 ($\text{M}+\text{H}$) $^+$.

[Referential Example 326]

Ethyl (1R*,3S*,4S*)-3-[(tert-butoxycarbonyl)amino]-4-
{[tert-butyl(diphenyl)silyl]oxy}cyclohexanecarboxylate:

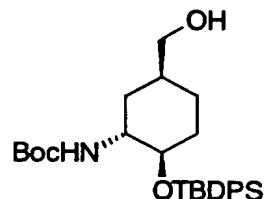


The compound (28.0 g) obtained in Referential Example
5 88 was dissolved in N,N-dimethylformamide (500 ml), and
tert-butyldiphenylsilyl chloride (63.5 ml) and imidazole
(19.9 g) were added. After the mixture was stirred at room
temperature for 10 hours, ethyl acetate and water were
added to the reaction mixture to conduct liquid separation.
10 The resultant water layer was extracted with ethyl acetate,
and organic layers were combined, washed twice with water
and dried over anhydrous sodium sulfate. After the solvent
was distilled off under reduced pressure, the residue was
purified by column chromatography on silica gel (methylene
15 chloride:methanol = 1:0 → 47:3) to obtain the title
compound (52.5 g) containing 0.4 molecules of N,N-
dimethylformamide.

¹H-NMR (CDCl₃) δ: 1.07(9H,s), 1.27(3H,t,J=7.1Hz),
1.38(9H,s), 1.43-1.59(3H,m), 1.63-1.67(1H,m), 1.92-
20 1.98(1H,m), 2.25-2.32(1H,m), 2.37-2.42(1H,m), 3.66(1H,br.s),
3.80(1H,br.s), 4.16(2H,q,J=7.1Hz), 4.32(1H,d,J=8.1Hz),
7.34-7.46(6H,m), 7.65-7.73(4H,m).

[Referential Example 327]

tert-Butyl (1R*,2R*,5S*)-2-[[tert-butyl(diphenyl)silyl]oxy]-5-(hydroxymethyl)cyclohexanecarbmate:

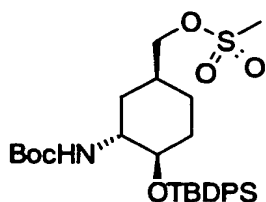


Lithium aluminum hydride (7.11 g) was suspended in
5 absolute diethyl ether (100 ml) at 0°C while purging with
argon, and a diethyl ether solution (500 ml) of the
compound (52.5 g) obtained in Referential Example 326 was
added dropwise over 30 minutes. After stirring at 0°C for
30 minutes, methanol (100 ml) was added dropwise to the
10 reaction mixture. The resultant slurry was removed by
filtration through Celite, and the filtrate was
concentrated. The residue was purified by column
chromatagraphy on silica gel (hexane:ethyl acetate = 3:1)
to obtain the title compound (29.6 g).

15 ¹H-NMR (CDCl₃) δ: 1.07(9H,s), 1.32-1.74(16H,m),
1.87(1H,t,J=10.4Hz), 3.35-3.55(2H,m), 3.71(1H,br.s),
3.79(1H,br.s), 4.36(1H,br.s), 7.34-7.44(6H,m), 7.65-
7.72(4H,m).

[Referential Example 328]

20 ((1R*,3S*,4S*)-3-[(tert-Butoxycarbonyl)amino]-4-[[tert-
butyl(diphenyl)silyl]oxy)cyclohexyl)methyl methane-
sulfonate:



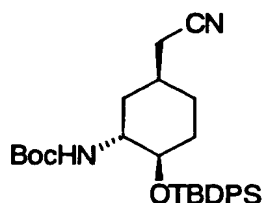
The compound (29.5 g) obtained in Referential Example 327 was dissolved in methylene chloride (200 ml) and pyridine (20 ml), and methanesulfonyl chloride (9.5 ml) was added to stir the mixture at room temperature for 6 hours. The solvent was distilled off under reduced pressure, and ethyl acetate and water were added to the residue to conduct liquid separation. The resultant water layer was extracted with ethyl acetate, and organic layers were combined, washed twice with water and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1) to obtain the title compound (29.8 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.08(9H,s), 1.38(9H,s), 1.43-1.61(5H,m), 1.86-1.89(2H,m), 3.02(3H,s), 3.77(1H,br.s), 3.81(1H,br.s), 4.10(2H,d,J=5.4Hz), 4.32(1H,br.s), 7.35-7.45(6H,m), 7.64-7.68(4H,m).

MS (ESI) m/z : 562($\text{M}+\text{H}$) $^+$.

[Referential Example 329]

tert-Butyl (1R*,2R*,5S*)-2-([tert-butyl(diphenyl)silyl]-oxy)-5-(cyanomethyl)cyclohexanecarbamate:

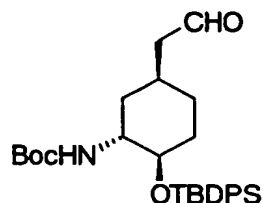


The compound (29.8 g) obtained in Referential Example 328 was dissolved in N,N-dimethylformamide (400 ml), and sodium cyanide (3.64 g) was added to stir the mixture at 80°C for 11 hours. Ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate were added to the reaction mixture to conduct liquid separation. The resultant water layer was extracted twice with ethyl acetate, and organic layers were combined, washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 5:1) to obtain the title compound (20.6 g).

¹H-NMR (CDCl₃) δ: 1.08 (9H,s), 1.38 (9H,s), 1.43-1.68 (5H,m), 1.79-1.85 (1H,m), 1.88-1.95 (1H,m), 2.32 (2H,d,J=7.1Hz), 3.77 (1H,br.s), 3.82 (1H,br.s), 4.32 (1H,br.d,J=6.8Hz), 7.35-7.45 (6H,m), 7.65-7.71 (4H,m).

[Referential Example 330]

tert-Butyl (1R*,2R*,5S*)-2-([tert-butyl(diphenyl)silyl]oxy)-5-(2-oxoethyl)cyclohexanecarbamate:

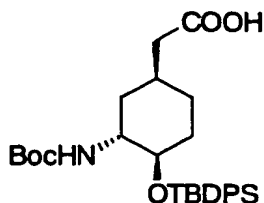


The compound (2.00 g) obtained in Referential Example 329 was dissolved in absolute methylene chloride (20 ml), and the system was purged with argon and then cooled to
 5 -78°C. To the solution, was added dropwise diisobutylaluminum hydride (0.95 M hexane solution, 8.55 ml). The temperature of the mixture was then allowed to raise to room temperature and stirred for 3 hours. The reaction mixture was cooled to 0°C, and methanol (10 ml)
 10 was added dropwise. The resultant slurry was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 1:0 → 49:1) to obtain the title
 15 compound (1.45 g).

¹H-NMR (CDCl₃) δ: 1.07(9H,s), 1.38(9H,s), 1.43-1.54(5H,m), 1.82-1.88(1H,m), 2.06(1H,br.s), 2.42-2.43(2H,m), 3.72(1H,br.s), 3.77(1H,br.s), 4.38(1H,br.s), 7.34-7.44(6H,m), 7.65-7.68(4H,m), 9.77(1H,t,J=1.7Hz).
 20 MS (FAB) m/z: 496(M+H)⁺.

[Referential Example 331]

2-((1R*,3S*,4S*)-3-[(tert-Butoxycarbonyl)amino]-4-{[tert-butyl(diphenyl)silyl]oxy}cyclohexyl)acetic acid:



The compound (8.40 g) obtained in Referential Example 330 was dissolved in a mixed solvent of water (33 ml) and tert-butanol (120 ml), and 2-methyl-2-butene (8.08 ml),
 5 sodium dihydrogenphosphate dihydrate (2.64 g) and sodium chlorite (3.45 g) were added to stir the mixture at room temperature for 1.5 hours. Methylene chloride and water were added to the reaction mixture to dilute it. The resultant water layer was adjusted to pH of about 4 with 1N
 10 hydrochloric acid. Liquid separation was conducted, and the resultant water layer was extracted twice with methylene chloride. Organic layers were combined and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was
 15 purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1 → 1:1) to obtain the title compound (7.62 g).

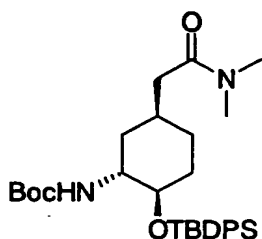
$^1\text{H-NMR}$ (CDCl_3) δ : 1.07(9H,s), 1.22-1.63(15H,m),
 1.82(1H,br.s), 2.17(1H,br.s), 2.27-2.33(1H,m),
 20 3.69(1H,br.s), 3.84(1H,br.s), 7.00(1H,br.s), 7.33-
 7.42(6H,m), 7.63-7.65(4H,m).

MS (ESI) m/z : 512 ($\text{M}+\text{H}$) $^+$.

[Referential Example 332]

tert-Butyl (1R*,2R*,5S*)-2-([tert-butyl(diphenyl)silyl]-

oxy)-5-[2-(dimethylamino)-2-oxoethyl]cyclohexanecarbamate:



The compound (7.62 g) obtained in Referential Example 331 was dissolved in N,N-dimethylformamide (150 ml), and
5 dimethylamine hydrochloride (6.07 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.56 g), 1-hydroxybenzotriazole monohydrate (1.01 g) and triethylamine (10.3 ml) were added to stir the mixture at room temperature for 4 days. The solvent was distilled off
10 under reduced pressure, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation. The resultant organic layer was extracted with methylene chloride, and organic layers were combined and dried over
15 anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 1:1). The solvent was distilled off, hexane was added to the residue, and formed white precipitate was collected by
20 filtration to obtain the title compound (6.42 g).

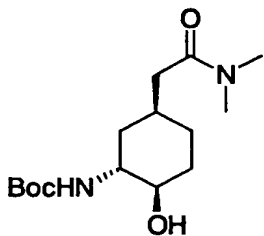
¹H-NMR (CDCl₃) δ: 1.08(9H,s), 1.38(9H,br.s), 1.43-1.55(5H,m), 1.79-1.86(1H,m), 2.03(1H,br.s), 2.21-2.32(2H,s), 2.94(3H,s), 3.03(3H,s), 3.74(1H,br.s), 3.80(1H,br.s),

4.49 (1H, br.s), 7.33-7.44 (6H, m), 7.64-7.69 (4H, m).

MS (ESI) m/z: 539 (M+H)⁺.

[Referential Example 333]

tert-Butyl (1R*,2R*,5S*)-5-[2-(dimethylamino)-2-oxoethyl]-
5 2-hydroxycyclohexanecarbamate:



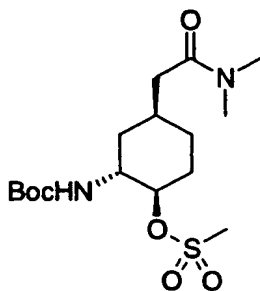
The compound (6.36 g) obtained in Referential Example 332 was dissolved in tetrahydrofuran (50 ml), and tetrabutylammonium fluoride (1N tetrahydrofuran solution,
10 17.85 ml) was added to stir the mixture at room temperature for 13 hours. The solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatography on silica gel (methylene chloride:methanol = 24:1) to obtain the title compound (3.49 g).

15 ¹H-NMR (CDCl₃) δ: 1.44 (9H, s), 1.46-1.60 (4H, m), 1.79-1.84 (2H, m), 2.28-2.35 (3H, s), 2.82 (1H, br.s), 2.95 (3H, s), 3.01 (3H, s), 3.56 (2H, br.s), 4.67 (1H, br.s).

MS (ESI) m/z: 301 (M+H)⁺.

[Referential Example 334]

20 ((1R*,2R*,4S*)-2-[(tert-Butoxycarbonyl)amino]-4-[2-(dimethylamino)-2-oxoethyl]cyclohexyl methanesulfonate:

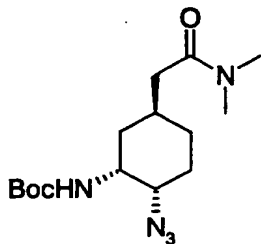


The compound (8.05 mg) obtained in Referential Example 333 was dissolved in methylene chloride (50 ml), and the solution was cooled to -78°C under an argon atmosphere to add dropwise methanesulfonyl chloride (2.70 ml). After the temperature of the mixture was allowed to raise to 0°C and stirred for 30 minutes, it was stirred at room temperature for 2 hours. Water was added to the reaction mixture to conduct liquid separation, and the resultant water layer was extracted with methylene chloride. Organic layers were combined, washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane:ethyl acetate = 1:1 \rightarrow 0:1) to obtain the title compound (3.63 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.43(9H,s), 1.59-1.74(4H,m), 1.85-2.30(5H,m), 2.95(3H,s), 3.00(3H,s), 3.10(3H,s), 3.79-3.83(1H,m), 4.72(1H,br.s), 4.91(1H,br.s).

MS (ESI) m/z : 379($\text{M}+\text{H}$) $^{+}$.

[Referential Example 335]
 tert-Butyl (1R*,2S*,5S*)-2-azido-5-[2-(dimethylamino)-2-oxoethyl]cyclohexanecarbamate:



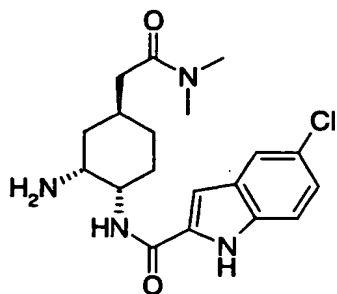
The compound (3.62 g) obtained in Referential Example 334 was dissolved in N,N-dimethylformamide (20 ml), and sodium azide (3.11 g) was added to stir the mixture at 75°C for 17 hours. The reaction mixture was poured into a mixed solvent of water and ethyl acetate to conduct liquid separation. The resultant water layer was extracted twice with ethyl acetate, and organic layers were combined, washed with water, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatography on silica gel (ethyl acetate) to obtain the title compound (1.30 g).

¹H-NMR (CDCl₃) δ: 1.14-1.21(1H,m), 1.33-1.40(1H,m), 1.45(9H,s), 1.61-1.71(1H,m), 1.78-1.91(3H,m), 2.22-2.27(3H,m), 2.94(3H,s), 3.00(3H,s), 3.60-3.62(1H,m), 3.97(1H,br.s), 4.76(1H,br.s).

MS (ESI) m/z: 326(M+H)⁺.

[Referential Example 336]

N-((1R*,2S*,4R*)-2-Amino-4-[2-(dimethylamino)-2-oxoethyl]-cyclohexyl)-5-chloroindole-2-carboxamide hydrochloride:



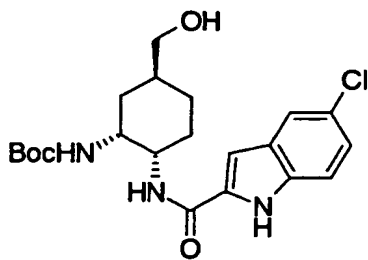
The title compound was obtained by treating, in a similar manner to Referential Example 69, a product obtained by catalytically reducing the compound obtained in Referential Example 335 in a similar manner to Referential Example 324 and then condensing it with 5-chloroindole-2-carboxylic acid.

¹H-NMR (DMSO-d₆) δ: 1.16-1.19(1H,m), 1.51-1.56(1H,m), 1.70-1.73(1H,m), 1.81-1.91(2H,m), 1.99-2.03(1H,m), 2.19-2.30(3H,m), 2.83(3H,s), 2.99(3H,s), 3.63(1H,br.s), 4.08(1H,br.s), 7.19(1H,dd,J=8.7,1.7Hz), 7.35(1H,s), 7.44(1H,d,J=8.7Hz), 7.69(1H,d,J=1.7Hz), 8.22(3H,br.s), 8.62(1H,d,J=7.1Hz), 11.91(1H,s).

MS (ESI) m/z: 377(M+H)⁺.

[Referential Example 337]

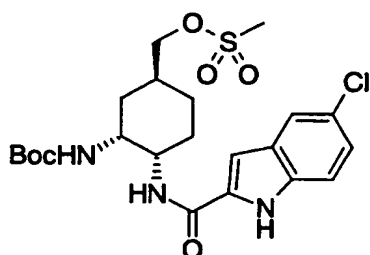
tert-Butyl (1R,2S,5S)-2-([(5-chloroindol-2-yl)carbonyl]-amino)-5-(hydroxymethyl)cyclohexanecarbamate:



The title compound was obtained from the compound obtained in Referential Example 97 in a similar manner to step 2) of Referential Example 129.

[Referential Example 338]

- 5 ((1S,3R,4S)-3-[(tert-butoxycarbonyl)amino]-4-[[(5-chloroindol-2-yl)carbonyl]amino)cyclohexyl)methyl methanesulfonate:



- The compound (500 mg) obtained in Referential Example 337 and triethylamine (329 ml) were suspended in tetrahydrofuran (8ml)-methylene chloride (8 ml), and the suspension was cooled to -78°C. After methanesulfonyl chloride (138 ml) was added dropwise to the suspension, the temperature of the suspension was gradually raised to -5°C, and the suspension was stirred for 15 hours at the same temperature. After the reaction mixture was concentrated, water was added to the residue to conduct extraction 3 times with methylene chloride. The resultant organic layers were washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure to obtain the title compound (654 mg).
- 10
15
20

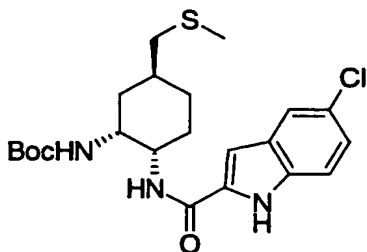
¹H-NMR (CDCl₃) δ: 1.57(9H,s), 1.84-2.01(4H,m), 2.28-

2.31 (1H,m), 3.04 (3H,s), 3.68 (1H,s), 3.74-3.75 (1H, m), 3.91-3.93 (1H,m), 4.02-4.12 (2H,m), 4.18-4.20 (1H,m), 4.85 (1H,br.s), 6.81 (1H,s), 7.21 (1H,dd,J=2.0,8.8Hz), 7.34 (1H,d,J=8.8Hz), 7.60 (1H,s), 8.02 (1H,br.s), 9.27 (1H,br.s).

5 MS (ESI) m/z: 500 (M+H)⁺.

[Referential Example 339]

tert-Butyl (1R,2S,5S)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-[(methylsulfanyl)methyl]cyclohexanecarbamate:



10 The compound (654 mg) obtained in Referential Example 338 was dissolved in N,N-dimethylformamide (8 ml), and a 15% aqueous solution (1.8 ml) of sodium thiomethoxide was added to stir the mixture at room temperature for 4 hours. The reaction mixture was poured into water and extracted 3
15 times with ethyl acetate. The resultant organic layers were washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by column chromatography on silica gel (methylene chloride:methanol =
20 24:1) to obtain the title compound (492 mg).

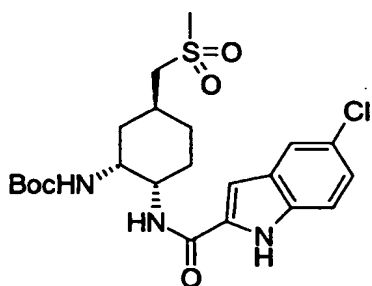
¹H-NMR (CDCl₃) δ: 1.52 (9H,s), 1.87-3.04 (13H,m), 3.91-3.94 (1H,m), 4.12-4.15 (1H,m), 4.95 (1H,br.s), 6.81 (1H,s), 7.19 (1H,dd,J=8.8,1.2Hz), 7.35 (1H,d,J=8.8Hz), 7.57 (1H,s),

9.82(1H,br.s).

MS (ESI) m/z: 452(M+H)⁺.

[Referential Example 340]

tert-Butyl (1R,2S,5S)-2-{[(5-chloroindol-2-yl)carbonyl]-
5-amino}-5-[(methylsulfonyl)methyl]cyclohexanecarbamate:

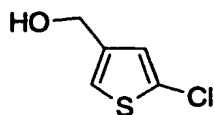


The compound (300 mg) obtained in Referential Example 339 was dissolved in methylene chloride (10 ml), and m-chloroperbenzoic acid (70%, 400 mg) was added at 0°C under stirring. After stirring was continued for 1 hour, as it is, the reaction mixture was poured into water and extracted 3 times with ethyl acetate. The resultant organic layers were washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated. After the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 24:1), liquid separation was conducted with a saturated aqueous solution of sodium hydrogencarbonate and ethyl acetate, and the resultant organic layer was concentrated to obtain the title compound (254 mg).

¹H-NMR (CDCl₃) δ: 1.44-2.19(13H,m), 2.22-2.30(2H,m), 2.89-3.25(7H,m), 3.93-4.15(2H,m), 4.98(1H,br.s), 6.82(1H,s),

7.21 (1H, dd, J=8.8, 2.0 Hz), 7.34 (1H, d, J=8.8 Hz), 7.60 (1H, br. s),
9.54 (1H, br. s).

[Referential Example 341] (5-Chlorothiophen-3-yl)methanol:

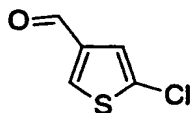


5 5-Chlorothiophene-3-carboxylic acid (Monatsh. Chem.,
Vol. 120, p. 53, 1989) (6.93 g) was dissolved in
tetrahydrofuran (750 ml), and triethylamine (27.3 ml) and
ethyl chloroformate (18.7 ml) were added to stir the
mixture at room temperature for 2.5 hours. An aqueous
10 solution (41 ml) of sodium borohydride (19.3 g) was added
dropwise over 10 minutes, and the mixture was stirred at
room temperature for 18.5 hours. After acetic acid was
added to the reaction mixture to acidify it, the solvent
was distilled off under reduced pressure. Water and
15 methylene chloride were added to the residue to conduct
liquid separation. The resultant organic layer was washed
with water and a saturated aqueous solution of sodium
hydrogencarbonate. After drying the organic layer, the
solvent was distilled off under reduced pressure. The
20 residue was purified by flash column chromatography on
silica gel (ethyl acetate:hexane = 1:4) to obtain the title
compound (5.17 g).

¹H-NMR (CDCl₃) δ: 1.63 (1H, t, J=5.8 Hz), 4.59 (2H, d, J=5.3 Hz),
6.91 (1H, d, J=1.7 Hz), 6.98-6.99 (1H, m).

25 [Referential Example 342]

5-Chlorothiophene-3-carbaldehyde:

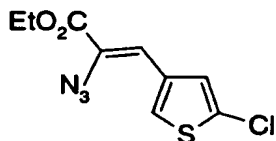


The compound (5.17 g) obtained in Referential Example 341 was dissolved in methylene chloride (400 ml), and
5 manganese dioxide (51.3 g) was added to stir the mixture at room temperature for 15 hours. After the reaction mixture was filtered, the solvent was distilled off under reduced pressure to obtain the title compound (2.84 g).

¹H-NMR (CDCl₃) δ: 7.35(1H,d,J=1.7Hz), 7.88(1H,d,J=1.7Hz),
10 9.75(1H,s).

[Referential Example 343]

Ethyl 2-azido-3-(5-chlorothiophen-3-yl)acrylate:



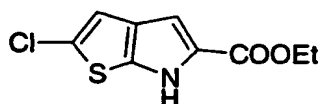
After ethanol (15 ml) was added to a 20% ethanol
15 solution (10.7 ml) of sodium ethoxide, and the mixture was cooled to 0°C, a mixture of the compound (1.01 g) obtained in Referential Example 342 and ethyl azidoacetate (3.55 g) was added dropwise over 30 minutes, and the resultant mixture was stirred at 0°C for 3 hours. A cooled aqueous
20 solution of ammonium chloride was added to the reaction mixture to conduct extraction 3 times with diethyl ether. Organic layers were combined, and the solvent was distilled

off under reduced pressure. The residue was purified by
flash column chromatography on silica gel (ethyl
acetate:hexane = 1:49) to obtain the title compound
(1.04 g).

5 ^1H -NMR (CDCl_3) δ : 1.38 (3H, t, $J=7.1\text{Hz}$), 4.34 (2H, q, $J=7.1\text{Hz}$),
6.75 (1H, s), 7.39 (1H, d, $J=1.7\text{Hz}$), 7.54 (1H, d, $J=1.7\text{Hz}$).

[Referential Example 344]

Ethyl 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylate:

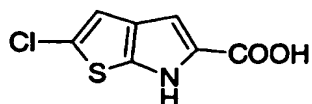


10 The compound (0.97 g) obtained in Referential Example
343 was dissolved in xylene (20 ml), and the solution was
heated under reflux for 30 minutes. After allowing the
reaction mixture to cool, the solvent was distilled off
under reduced pressure. Hexane was added to the residue,
15 solids formed were collected by filtration to obtain the
title compound (0.608 g).

^1H -NMR (CDCl_3) δ : 1.38 (3H, t, $J=7.0\text{Hz}$), 4.35 (2H, q, $J=7.0\text{Hz}$),
6.90 (1H, s), 7.00 (1H, d, $J=1.9\text{Hz}$), 9.32 (1H, br).

[Referential Example 345]

20 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid:



The title compound was obtained from the compound
obtained in Referential Example 344 in a similar manner to

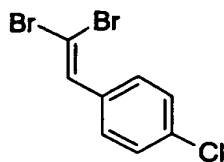
Referential Example 274.

$^1\text{H-NMR}$ (CD_3OD) δ : 3.35(1H,s), 6.94(1H,s), 6.96(1H,s).

MS (ESI) m/z : 200(M-H) $^-$.

[Referential Example 346]

5 1-Chloro-4-(2,2-dibromovinyl)benzene:



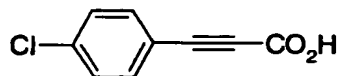
4-Chlorobenzaldehyde (2.81 g) was dissolved in methylene chloride (300 ml), and carbon tetrabromide (13.3 g) and triphenylphosphine (21.0 g) were added to stir the mixture at room temperature for 90 minutes. After insoluble matter deposited was removed by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 20:1) to obtain the title compound
15 (5.54 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 7.33(2H,d, $J=8.5\text{Hz}$), 7.43(1H,s), 7.47(2H,d, $J=8.5\text{Hz}$).

MS (EI) m/z : 296(M^+).

[Referential Example 347]

20 3-(4-Chlorophenyl)-2-propiolic acid:



The compound (1.0 g) obtained in Referential Example

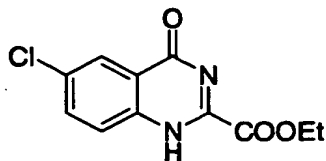
346 was dissolved in tetrahydrofuran (30 ml), and n-butyllithium (1.59 N hexane solution, 4.46 ml) was added dropwise at -78°C under an argon atmosphere. The temperature of the reaction mixture was allowed to raise to room temperature and stirred for 1 hour. The reaction mixture was cooled again to -78°C, stirred for 2 minutes under a carbon dioxide atmosphere and then warmed to room temperature. After the reaction mixture was concentrated under reduced pressure, saturated aqueous solution of sodium chloride and ethyl acetate were added to the residue to conduct liquid separation. 3N Hydrochloric acid was added to the resultant water layer to acidify it, and extraction was conducted with ethyl acetate. The resultant organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the title compound (453 mg).

$^1\text{H-NMR}$ (DMSO- d_6) δ : 7.55 (2H, d, $J=8.5\text{Hz}$), 7.66 (2H, d, $J=8.5\text{Hz}$), 13.90 (1H, br. s).

MS (EI) m/z : 180 (M^+).

[Referential Example 348]

Ethyl 6-chloro-4-oxo-1,4-dihydroquinazoline-2-carboxylate:



Ethyl chlorooxoacetate (2.0 ml) was added to a solution of 2-amino-5-chlorobenzamide (2.50 g) in pyridine

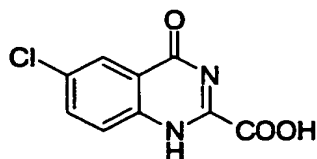
(15 ml), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure, and the resultant residue was dissolved in acetic acid (50 ml). Acetic anhydride (5.0 ml) was
5 added to the solution, and the mixture was heated under reflux for 16 hours. The solvent was distilled off under reduced pressure, and ethanol was added to the residue. Crystals deposited were collected by filtration and washed to obtain the title compound (2.71 g).

10 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.35 (3H, t, $J=7.1\text{Hz}$), 4.38 (2H, q, $J=7.1\text{Hz}$), 7.85 (1H, d, $J=8.6\text{Hz}$), 7.91 (1H, dd, $J=8.6, 2.3\text{Hz}$), 8.10 (1H, d, $J=2.3\text{Hz}$), 12.85 (1H, br. s).

MS (ESI) m/z : 253 ($\text{M}+\text{H}$) $^+$.

[Referential Example 349]

15 6-Chloro-4-oxo-1,4-dihydroquinazoline-2-carboxylic acid:



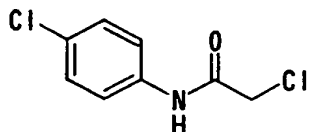
Lithium hydroxide (263 mg) was added to a solution of the compound (1.26 g) obtained in Referential Example 348 in a mixed solvent of water (5 ml) and tetrahydrofuran (15
20 ml), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was neutralized with 1N hydrochloric acid (11 ml) under ice cooling and stirred for 1 hour. Crystals deposited were collected by filtration and washed with water to obtain the title compound (0.96 g).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 7.50-8.20 (3H,m), 12.44 (1H,br.s).

MS (ESI) m/z : 265 ($\text{M}+\text{H}+\text{CH}_3\text{CN}$) $^+$.

[Referential Example 350]

2-Chloro-N-(4-chlorophenyl)acetamide:



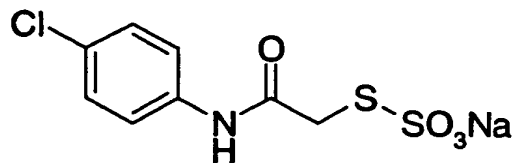
5

p-Chloroaniline (3.82 g) was dissolved in ethyl acetate (30 ml), and chloroacetyl chloride (2.39 ml) was added at room temperature to stir the mixture for 1 hour. After the reaction mixture was heated and stirred at 60°C for 3.5 hours, crystals deposited were collected by filtration to obtain the title compound (4.78 g). The filtrate was concentrated to about 1/4, and crystals deposited were collected by filtration to obtain the title compound (1.01 g).

15 $^1\text{H-NMR}$ (CDCl_3) δ : 4.19 (2H,s), 7.33 (2H,d,J=9.0Hz), 7.51 (2H,d,J=9.0Hz), 8.22 (1H,br.s).

[Referential Example 351]

Sodium S-[2-(4-chloroanilino)-2-oxoethyl]thiosulfate:



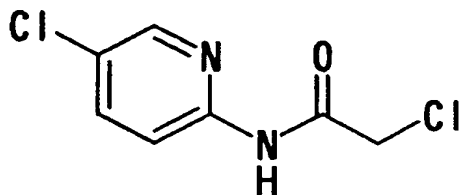
20 The compound (5.79 g) obtained in Referential Example

350 was dissolved in ethanol (140 ml), and an aqueous solution (140 ml) of sodium thiosulfate pentahydrate (7.04 g) was added at a time at 70°C to heat the mixture under reflux for 1.5 hours. The reaction mixture was concentrated to about 1/10, and crystals deposited were collected by filtration to obtain the title compound (8.20 g).

¹H-NMR (DMSO-d₆) δ: 3.73(2H,s), 7.35(2H,d,J=8.8Hz), 7.57(2H,d,J=8.8Hz), 10.30(1H,s).

[Referential Example 352]

2-Chloro-N-(5-chloropyridin-2-yl)acetamide hydrochloride:

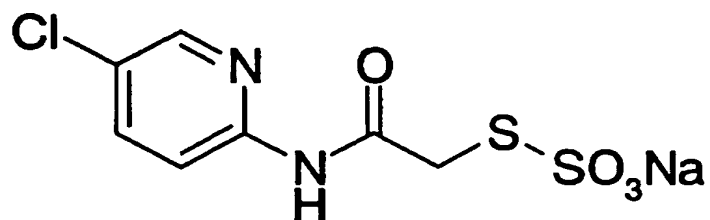


2-Amino-5-chloropyridine (3.85 g) was dissolved in ethyl acetate (60 ml), and chloroacetyl chloride (2.39 ml) was added at room temperature to stir the mixture for 1 hour. After the reaction mixture was heated and stirred at 60°C for 30 minutes, chloroacetyl chloride (0.5 ml) was additionally added, and the mixture was stirred at 60°C for additional 1 hour. Powder deposited was collected by filtration to obtain the title compound (6.18 g).

¹H-NMR (DMSO-d₆) δ: 4.36(2H,s), 7.94(1H,dd,J=8.8,2.7Hz), 8.09(1H,d,J=8.8Hz), 8.40(1H,d,J=2.7Hz), 11.03(1H,s).

[Referential Example 353]

Sodium S-{2-[(5-chloropyridin-2-yl)amino]-2-oxoethyl}thiosulfate:



An aqueous solution (130 ml) with sodium thiosulfate
5 pentahydrate (6.35 g) and sodium hydrogencarbonate (2.15 g)
dissolved therein was added to a solution with the compound
(6.18 g) obtained in Referential Example 352 dissolved in

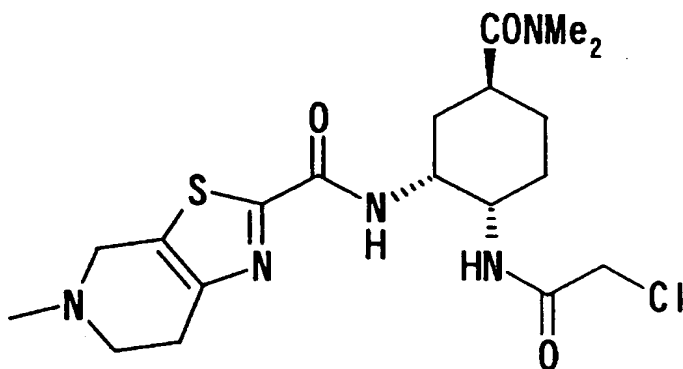
ethanol (130 ml) at a time at 80°C under stirring, and the mixture was heated under reflux at 110°C for 2 hours. The reaction mixture was concentrated to solids under reduced pressure, and ethanol (500 ml) was added to the residue.

5 The resultant mixture was heated and extracted twice. The extract was concentrated to about 1/20, and diethyl ether was added. Insoluble matter deposited was collected by filtration to obtain the title compound (6.65 g).

¹H-NMR (DMSO-d₆) δ: 3.77(2H,s), 7.89(1H,dd,J=9.0,2.7Hz),
10 8.09(1H,d,J=9.0Hz), 8.34(1H,d,J=2.7Hz), 10.57(1H,s).

[Referential Example 354]

N-{(1R,2S,5S)-2-[(2-chloroacetyl)amino]-5-
[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-
tetrathiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



15

The compound (100 mg) obtained in Referential Example 253 was dissolved in ethyl acetate (10 ml), and chloroacetyl chloride (21.6 μl) was added to heat and stir the mixture at 60°C for 30 minutes. After allowing the
20 reaction mixture to cool, insoluble matter was collected

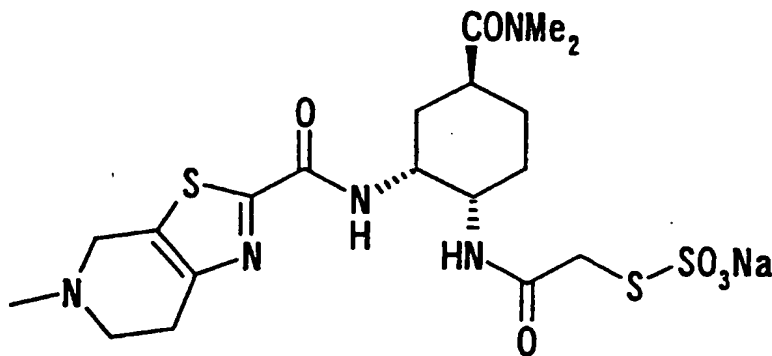
by filtration and dissolved in methylene chloride-methanol, and the solvent was distilled off under reduced pressure to obtain the crude title compound (112 mg).

¹H-NMR (DMSO-d₆) δ: 1.35-1.50(1H,m), 1.55-2.00(5H,m),
5 2.78(3H,s), 2.98(3H,s), 3.00-3.25(5H,m), 3.17(3H,s), 3.80-
3.90(1H, m), 3.96(1H,d,J=12.9Hz), 4.00-4.15(1H,m),
4.02(1H,d,J=12.9Hz), 4.45-4.70(2H,m), 7.85-8.00(1H,br),
8.12(1H,d,J=7.3Hz), 8.35(1H,d,J=8.3Hz).

MS (ESI) m/z: 442(M+H)⁺.

10 [Referential Example 355]

Sodium S-{2-[(1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-
{[(5-methyl-4,5,6,7-tetrathiazolo[5,4-c]pyridine-2-yl)-
carbonyl]amino}cyclohexyl)amino]-2-oxoethyl}thiosulfate:



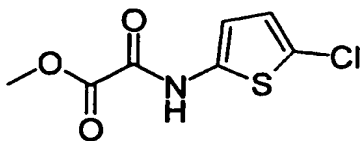
15 The compound (106 mg) obtained in Referential Example
354 was dissolved in ethanol (1.5 ml), and an aqueous
solution (1.5 ml) of sodium thiosulfate pentahydrate (55
mg) and sodium hydrogencarbonate (18.6 mg) dissolved
therein was added at a time at 90°C under stirring. The
20 resultant mixture was heated under reflux for 1 hour. The

reaction mixture was concentrated to solids under reduced pressure, and ethanol (10 ml) was added to the residue. The resultant mixture was heated and extracted. The extract was concentrated to about 1/2, and isopropyl ether (10 ml) was added. Insoluble matter deposited was collected by filtration to obtain the title compound (72 mg).

¹H-NMR (DMSO-d₆) δ: 1.35-1.50 (1H,m), 1.55-1.90 (5H,m), 2.40 (3H,s), 2.78 (3H,s), 2.80-3.10 (5H,m), 2.96 (3H,s), 3.44 (1H,d,J=14.2Hz), 3.50 (1H,d,J=14.2Hz), 3.68 (2H,s), 3.75-3.90 (1H,m), 4.45-4.50 (1H,m), 8.01 (1H,d,J=7.4Hz), 8.15 (1H,d,J=8.3Hz).

[Referential Example 356]

Methyl 2-[(5-chlorothiophen-2-yl)amino]-2-oxoacetate:



15

Triethylamine (1.25 ml) and diphenylphosphoryl azide (1.55 ml) were added to a suspension of 5-chlorothiophene-2-carboxylic acid (0.99 g) in toluene (20 ml), and the mixture was stirred at 80°C for 1 hour. After the reaction mixture was cooled to room temperature, tert-butanol (2 ml) was added, and the mixture was heated under reflux for 19 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride (200 ml) was added to the resultant residue. The resultant mixture was

successively washed with distilled water, a 10% aqueous solution of citric acid, distilled water, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over
5 anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain tert-butyl 5-chloro-2-thienylcarbamate (1.05 g).

10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.51(9H,s), 6.21(1H,d,J=3.1Hz), 6.60(1H,d,J=3.1Hz), 6.91(1H,br.s).

MS (ESI) m/z : 234(M+H) $^+$.

After the product (1.87 g) obtained above was added to a 4N dioxane solution (40 ml) of hydrochloric acid, and
15 the mixture was stirred at room temperature for 4 hours, the solvent was distilled off under reduced pressure. The residue was suspended in tetrahydrofuran (50 ml), and sodium hydrogencarbonate (2.02 g) and methyl chlorooxoacetate (0.883 ml) were added under ice cooling
20 to stir the mixture at room temperature for 18 hours. After the solvent was distilled off under reduced pressure, and water and methylene chloride were added to the residue to conduct liquid separation, the resultant organic layer was washed with saturated aqueous solution of sodium
25 chloride and dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel

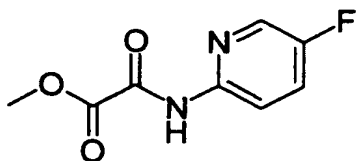
(hexane:ethyl acetate = 3:1), and the solvent was distilled off to obtain the title compound (1.44 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 3.98 (3H, s), 6.61 (1H, d, $J=4.2\text{Hz}$), 6.75 (1H, d, $J=4.2\text{Hz}$), 9.42 (1H, br. s).

5 MS (FAB) m/z : 220 ($\text{M}+\text{H}$) $^+$.

[Referential Example 357]

Methyl 2-[(5-fluoropyridin-2-yl)amino]-2-oxoacetate:



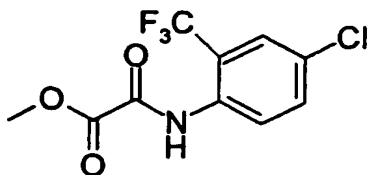
The title compound was obtained from 2-amino-5-fluoropyridine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.99 (3H, s), 7.48-7.53 (1H, m), 8.21 (1H, d, $J=2.9\text{Hz}$), 8.27-8.31 (1H, m), 9.41 (1H, br. s).

MS (FAB) m/z : 198 ($\text{M}+\text{H}$) $^+$.

15 [Referential Example 358]

Methyl 2-[4-chloro-2-(trifluoromethyl)anilino]-2-oxoacetate:



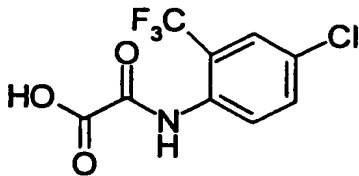
The title compound was obtained from 4-chloro-2-trifluoroaniline and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.01 (3H, s), 7.58 (1H, dd, $J=8.8, 2.2\text{Hz}$),
7.65 (1H, d, $J=2.2\text{Hz}$), 8.34 (1H, d, $J=8.8\text{Hz}$), 9.30 (1H, br. s).

MS (EI) m/z : 281 ($\text{M}+\text{H}$) $^+$.

[Referential Example 359]

5 2-[4-Chloro-2-(trifluoromethyl)anilino]-2-oxoacetic acid:



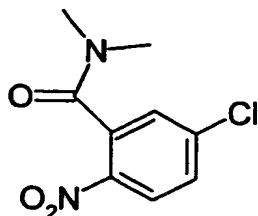
Lithium hydroxide (28 mg) was added to a solution of the compound (297 mg) obtained in Referential Example 358 in a mixed solvent of tetrahydrofuran (7ml) and water (3
10 ml), and the mixture was stirred at room temperature for 2 hours. 1N Hydrochloric acid (8 ml) and methylene chloride (20 ml) were added to the reaction mixture to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was
15 distilled off under reduced pressure, and the residue was dried to obtain the title compound (291 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 7.61 (1H, dd, $J=8.8, 2.5\text{Hz}$),
7.68 (1H, d, $J=2.5\text{Hz}$), 8.26 (1H, d, $J=8.8\text{Hz}$), 9.36 (1H, br. s).

MS (ESI, anion) m/z : 267 ($\text{M}-\text{H}$) $^-$

20 [Referential Example 360]

5-Chloro-N,N-dimethyl-2-nitrobenzamide:

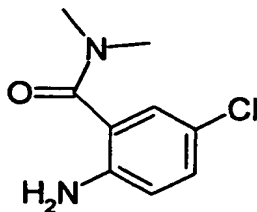


The title compound was obtained by condensing 5-chloro-2-nitrobenzoic acid with dimethylamine in a similar manner to the process described in Referential Example 143.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 2.86(3H,s), 3.16(3H,s),
7.38(1H,d,J=2.2Hz), 7.51(1H,dd,J=8.8,2.2Hz),
8.15(1H,d,J=8.8Hz).

[Referential Example 361]

2-Amino-5-chloro-N,N-dimethylbenzamide:



10

Iron(III) chloride hexahydrate (9.93 g) and zinc powder (8.01 g) were added to a solution of the compound (2.8 g) obtained in Referential Example 360 in a mixed solvent of N,N-dimethylformamide (80 ml) and water (40 ml),
15 and the mixture was heated under reflux for 20 minutes. The reaction mixture was filtered through Celite 545, and ethyl acetate (200 ml) was added to the filtrate to conduct liquid separation. The resultant water layer was washed with ethyl acetate (100 ml x 2), and organic layers

were combined, washed with distilled water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was subjected to column chromatography on silica gel

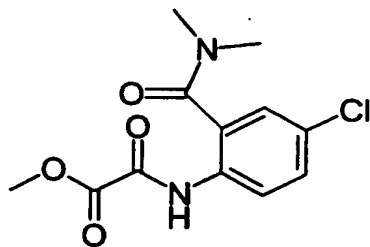
5 (methylene chloride:hexane = 1:1 → 1:0 → methanol:methylene chloride = 1:100) to obtain the title compound (2.41 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 3.13(6H,s), 4.33(2H,br),
6.65(1H,d,J=8.5Hz), 7.07(1H,d,J=2.2Hz),
10 7.11(1H,dd,J=8.5,2.2Hz).

MS (ESI) m/z : 240 ($\text{M}+\text{MeCN}$) $^+$.

[Referential Example 362]

Methyl 2-{4-chloro-2-[(dimethylamino)carbonyl]anilino}-2-oxoacetate:



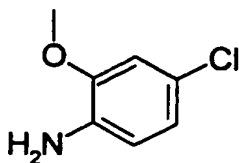
15

The title compound was obtained from the compound obtained in Referential Example 361 and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

20 $^1\text{H-NMR}$ (CDCl_3) δ : 3.09(6H,br), 3.96(3H,s),
7.30(1H,d,J=2.4Hz), 7.41(1H,d,J=8.8,2.4Hz),
8.34(1H,d,J=8.8Hz), 10.46(1H,br).

MS (ESI) m/z : 285 ($\text{M}+\text{H}$) $^+$.

[Referential Example 363] 4-Chloro-2-methoxyaniline:



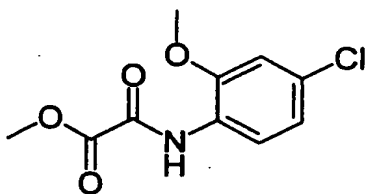
The title compound was obtained from 5-chloro-2-nitroanisole in a similar manner to the process described
5 in Referential Example 361.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.65-3.95 (2H, br), 3.87 (3H, s),
6.61 (1H, d, $J=8.8\text{Hz}$), 6.74-6.78 (2H, m).

MS (ESI) m/z : 199 ($\text{M}+\text{MeCN}+\text{H}$) $^+$.

[Referential Example 364]

10 Methyl 2-(4-chloro-2-methoxyanilino)-2-oxoacetate:



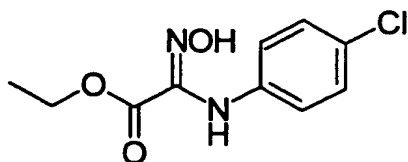
The title compound was obtained from the compound
obtained in Referential Example 363 and methyl
chlorooxoacetate in a similar manner to the process
15 described in Referential Example 242.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.92 (3H, s), 3.97 (3H, s),
6.90 (1H, d, $J=2.2\text{Hz}$), 6.98 (1H, dd, $J=8.8, 2.2\text{Hz}$),
8.35 (1H, d, $J=8.8\text{Hz}$), 9.33-9.44 (1H, br).

MS (ESI) m/z : 244 ($\text{M}+\text{H}$) $^+$.

20 [Referential Example 365]

Ethyl 2-(4-chloroanilino)-2-(hydroxyimino)-acetate:



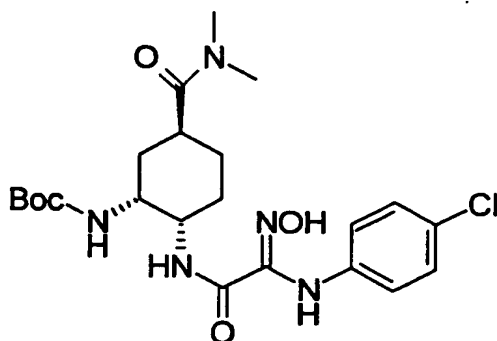
The title compound was obtained from 4-chloroaniline (3.03 g) and ethyl 2-chloro-2-hydroxyiminoacetate in a similar manner to the process described in literature (Gilchrist, T. L.; Peek, M. E.; Rees, C. W.; J. Chem. Soc. Chem. Commun., 1975, 913).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.26 (3H, t, $J=7.1\text{Hz}$), 1.60-1.80 (1H, br), 4.28 (2H, q, $J=7.1\text{Hz}$), 6.85 (2H, d, $J=8.6\text{Hz}$), 7.24 (2H, d, $J=8.6\text{Hz}$), 8.15-8.45 (1H, br).

MS (ESI) m/z : 243 ($\text{M}+\text{H}$) $^+$.

[Referential Example 366]

tert-Butyl (1R,2S,5S)-2-{[2-(4-chloroanilino)-2-(hydroxyimino)acetyl]amino}-5-[(dimethylamino)carbonyl]-cyclohexylcarbamate:



15

The compound (597 mg) obtained in Referential Example 144 was added to a solution of the compound (350 mg) obtained in Referential Example 365 in ethanol (5.0 ml),

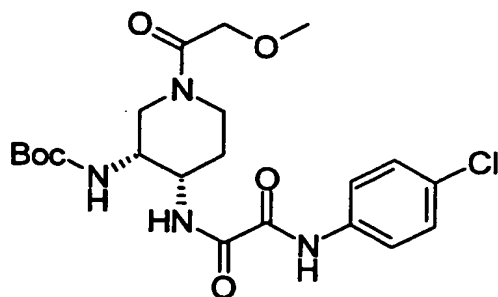
and the mixture was stirred at 70°C for 3 days. After the reaction mixture was concentrated under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 30:1) to obtain
5 the title compound (180 mg).

¹H-NMR (CD₃OD) δ: 1.46(9H,s), 1.47-1.84(6H,m), 1.88-1.95(1H,m), 2.90(3H,s), 3.08(3H,s), 3.90-3.97(1H,m), 4.11-4.17(1H,m), 6.84(2H,d,J=8.8Hz), 7.18(2H,d,J=8.8Hz).

MS (ESI) m/z: 504 (M+Na)⁺.

10 [Referential Example 367]

tert-Butyl (3R,4S)-4-{[2-(4-chloroanilino)-2-oxoacetyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:



15 The title compound was obtained from the compound obtained in Referential Example 374 and the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.

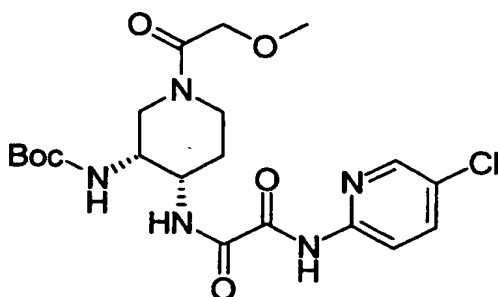
¹H-NMR (CDCl₃) δ: 1.45(9H,s), 1.55-1.75(1H,br), 1.94-2.07(1H,br), 2.70-3.00(1H,m), 3.10-3.37(1H,m), 3.44(3H,s),
20 3.88-4.22(4H,m), 4.55-4.69(1H,br), 4.80-4.90(0.5H,br), 5.36-5.48(0.5H,br), 7.20-7.30(1H,br), 7.32(2H,d,J=8.8Hz),

7.62 (2H, d, J=8.8 Hz), 8.20-8.40 (1H, br), 9.15-9.25 (1H, br).

MS (ESI) m/z: 469 (M+H)⁺.

[Referential Example 368]

tert-Butyl (3R,4S)-4-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:



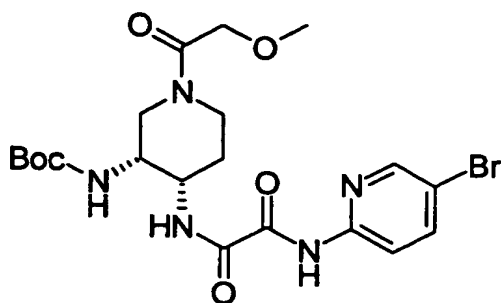
The title compound was obtained from the compound obtained in Referential Example 266 and the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.

¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 1.65-2.30 (2H, br), 2.68-3.02 (1H, m), 3.10-3.35 (1H, m), 3.44 (3H, s), 3.80-4.25 (4H, m), 4.45-4.70 (1H, m), 5.05-5.20 (0.5H, m), 5.80-5.93 (0.5H, m), 7.30-7.40 (1H, br), 7.71 (1H, br d, J=8.7 Hz), 7.95-8.05 (0.3H, br), 8.19 (1H, br d, J=8.8 Hz), 8.31 (1H, br. s), 8.38-8.53 (0.7H, br), 9.74-9.84 (1H, br).

MS (ESI) m/z: 470 (M+H)⁺.

[Referential Example 369]

tert-Butyl (3R,4S)-4-({2-[(5-bromopyridin-2-yl)amino]-2-oxoacetyl}amino)-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:

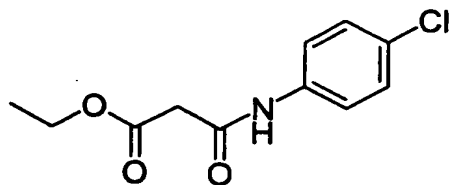


The title compound was obtained from the compound
 obtained in Referential Example 375 and the compound
 obtained in Referential Example 220 in a similar manner to
 5 the process described in Referential Example 214.

¹H-NMR (CDCl₃) δ: 1.47(9H,s), 1.50-1.75(1H,m), 1.95-
 2.13(1H,br), 2.70-2.98(1H,m), 3.05-3.36(1H,m),
 3.45(3H,s), 3.80-4.24(4H,m), 4.57-4.73(1H,br), 4.85-
 4.95(0.25H,br), 5.10-5.15(0.25H,br), 5.45-5.58(0.5H,br),
 10 7.30-7.38(1H,m), 7.84(1H,dd,J=8.8,2.2Hz),
 8.16(1H,d,J=8.8Hz), 8.30-8.55(1H,br), 8.40(1H,d,J=2.2Hz),
 9.68(1H,br.s).

[Referential Example 370]

Ethyl 3-(4-chloroanilino)-3-oxopropionate:



15

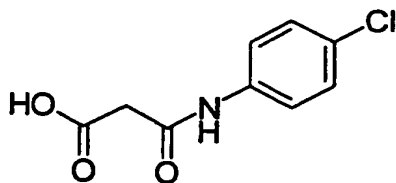
Potassium ethyl malonate (3.2 g), 1-hydroxy-
 benzotriazole (2.1 g) and 1-(3-dimethylaminopropyl)-3-
 ethylcarbodiimide hydrochloride (4.5 g) were successively
 added to a solution of 4-chloroaniline (2.0 g) in N,N-

dimethylformamide (20 ml) at room temperature, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium

- 5 hydrogencarbonate, a 10% aqueous solution of citric acid and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain the title compound (4.0 g).
- 10 $^1\text{H-NMR}$ (CDCl_3) δ : 1.33(3H,t,J=7.3Hz), 3.47(2H,s), 4.26(2H,q,J=7.3Hz), 7.29(2H,d,J=8.8Hz), 7.51(2H,d,J=8.8Hz), 9.32(1H,br.s).

[Referential Example 371]

3-(4-Chloroanilino)-3-oxopropionic acid:



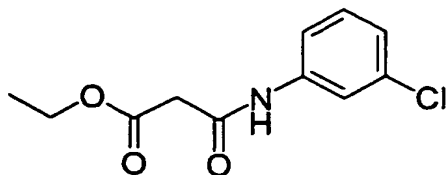
- 15 A 1N aqueous solution (10 ml) of sodium hydroxide was added dropwise to a solution of the compound (1.0 g) obtained in Referential Example 370 in ethanol (10 ml) at room temperature, and the mixture was stirred for 2 hours.
- 20 1N Hydrochloric acid (10 ml) was added to the reaction mixture, the mixture was stirred, and insoluble matter deposited was then collected by filtration to obtain the title compound (0.5 g).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.34(2H,s), 7.35(2H,d,J=8.8Hz),

7.59(2H,d,J=8.8Hz), 10.26(1H,s), 12.66(1H,br.s).

[Referential Example 372]

Ethyl 3-(3-chloroanilino)-3-oxopropionate:

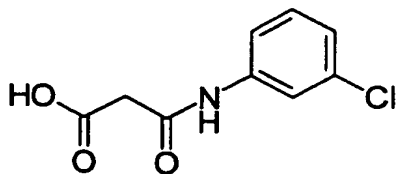


5 The title compound was obtained by condensing 3-chloroaniline with potassium ethyl malonate in a similar manner to the process described in Referential Example 370.

¹H-NMR (CDCl₃) δ: 1.33(3H,t,J=7.3Hz), 3.47(2H,s),
4.26(2H,q,J=7.3Hz), 7.09(1H,d,J=8.8Hz), 7.22-7.26(1H,m),
10 7.39(1H,d,J=8.8Hz), 7.69(1H,s), 9.35(1H,br.s).

[Referential Example 373]

3-(3-Chloroanilino)-3-oxopropionic acid:

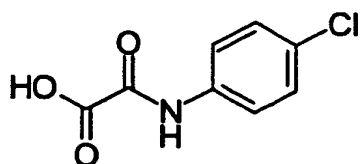


15 The title compound was obtained from the compound obtained in Referential Example 372 in a similar manner to the process described in Referential Example 371.

¹H-NMR (DMSO-d₆) δ: 3.35(2H,s), 7.11(1H,d,J=8.8Hz),
7.33(1H,t,J=8.8Hz), 7.39(1H,d,J=8.8Hz), 7.78(1H,s),
10.31(1H,s), 12.67(1H,br.s).

20 [Referential Example 374]

2-(4-Chloroanilino)-2-oxoacetic acid:

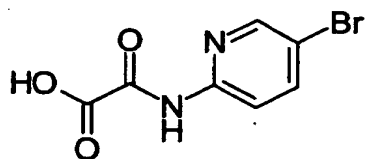


The title compound was obtained from the compound obtained in Referential Example 242 in a similar manner to the process described in Referential Example 359.

- 5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 7.37 (2H, d, $J=8.8\text{Hz}$), 7.79 (2H, d, $J=8.8\text{Hz}$), 10.66 (1H, s).

[Referential Example 375]

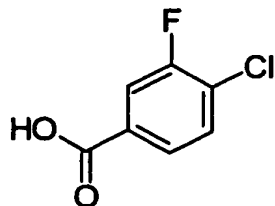
2-[(5-Bromopyridin-2-yl)amino]-2-oxoacetic acid:



- 10 The title compound was obtained from the compound obtained in Referential Example 262 in a similar manner to the process described in Referential Example 359.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 7.95-8.00 (1H, m), 8.08 (1H, dd, $J=8.8, 2.0\text{Hz}$), 8.50 (1H, d, $J=2.0\text{Hz}$), 10.74 (1H, s).

- 15 [Referential Example 376] 4-Chloro-3-fluorobenzoic acid:



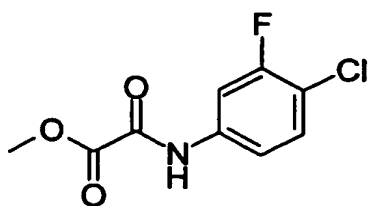
Sodium chlorite (17 g) was added portionwise to a mixture solution composed of 4-chloro-3-fluorobenzaldehyde

(10 g), amidosulfuric acid (18 g), tert-butyl alcohol (50 ml) and water (50 ml) under ice cooling, and the mixture was stirred for 4 days while the temperature of the system was gradually raised to room temperature. The reaction mixture was diluted with ethyl acetate and washed with water, 1N hydrochloric acid and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure, the resultant residue was recrystallized from a mixed solvent of diisopropyl ether and hexane to obtain the title compound (11.2 g).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 7.72 (1H, dt, $J=8.3, 1.5\text{Hz}$), 7.77 (1H, dt, $J=8.3, 1.6\text{Hz}$), 7.82 (1H, dt, $J=9.7, 1.5\text{Hz}$), 13.45 (1H, s).

[Referential Example 377]

Methyl 2-(4-chloro-3-fluoroanilino)-2-oxoacetate:



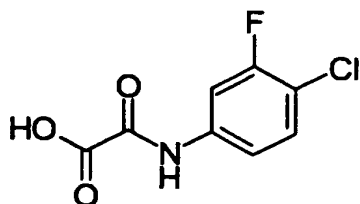
The title compound was obtained by subjecting the compound obtained in Referential Example 376 to Curtius rearrangement reaction and then condensing this product with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 356.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.99 (3H, s), 7.25-7.27 (1H, m),

7.39 (1H, t, J=8.5Hz), 7.72 (1H, dd, J=10.4, 2.4Hz),
8.90 (1H, br. s).

[Referential Example 378]

2-(4-Chloro-3-fluoroanilino)-2-oxoacetic acid:



5

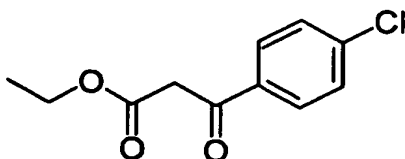
The title compound was obtained from the compound obtained in Referential Example 377 in a similar manner to the process described in Referential Example 359.

¹H-NMR (DMSO-d₆) δ: 7.52 (1H, t, J=8.8Hz),

10 7.63 (1H, dd, J=8.8, 2.2Hz), 7.88 (1H, dd, J=12.0, 2.2Hz),
10.83 (1H, br. s).

[Referential Example 379]

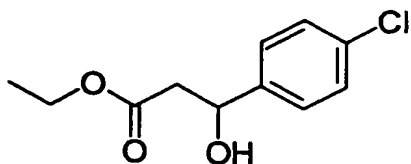
Ethyl 3-(4-chlorophenyl)-3-oxopropionate:



15 Triethylamine (17 ml) and magnesium chloride (5.5 g) were added to a suspension of potassium ethyl malonate (8.2 g) in ethyl acetate (100 ml) under ice cooling, and the mixture was stirred for 18 hours while the temperature of the system was gradually raised to room temperature. On
20 the other hand, a suspension composed of 4-chlorobenzoic acid (5.0 g), thionyl chloride (12 ml), N,N-

dimethylformamide (one drop) and toluene (100 ml) was heated under reflux for 1 hour, and the reaction mixture was then concentrated. The resultant residue was dissolved in ethyl acetate, and the solution was added dropwise to the reaction mixture previously prepared under ice cooling. The resultant mixture was stirred for 18 hours while the temperature of the system was gradually raised to room temperature. A 10% aqueous solution of citric acid was added to the reaction mixture, and the mixture was stirred for 30 minutes to separate the resultant organic layer. The organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was isolated and purified by column chromatography on silica gel (chloroform) to obtain the title compound (6.4 g).
 $^1\text{H-NMR}$ (CDCl_3) δ : 1.26(3H,t,J=7.3Hz), 3.96(2H,s), 4.21(2H,q,J=7.3Hz), 7.46(2H,d,J=8.8Hz), 7.89(2H,d,J=8.8Hz).
[Referential Example 380]

Ethyl 3-(4-chlorophenyl)-3-hydroxypropionate:



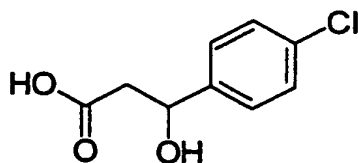
Sodium borohydride (0.2 g) was added portionwise under ice cooling to a solution of the compound (1.0 g) obtained in Referential Example 379 in tetrahydrofuran (10

ml), and the mixture was stirred for 2 hours while the temperature of the system was gradually raised to room temperature. A 10% aqueous solution of citric acid was added to the reaction mixture, and the resultant mixture was extracted with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was isolated and purified by column chromatography on silica gel (chloroform) to obtain the title compound (0.56 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.27 (3H, t, $J=7.3\text{Hz}$), 2.70 (1H, d, $J=7.8\text{Hz}$), 2.71 (1H, d, $J=3.4\text{Hz}$), 3.37 (1H, d, $J=3.4\text{Hz}$), 4.18 (2H, q, $J=7.3\text{Hz}$), 5.09–5.13 (1H, m), 7.30–7.35 (5H, m).

[Referential Example 381]

3-(4-Chlorophenyl)-3-hydroxypropionic acid:



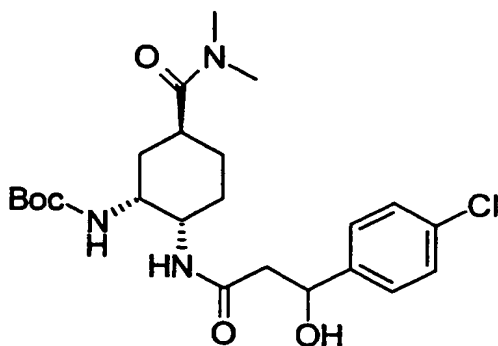
The title compound was obtained from the compound obtained in Referential Example 380 in a similar manner to the process described in Referential Example 359.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.25–3.32 (1H, m), 4.89–4.95 (1H, m), 5.45–5.53 (1H, m), 7.35–7.36 (5H, m), 12.11–12.18 (1H, m).

MS (ESI, anion) m/z : 198 (M-H) $^-$.

[Referential Example 382]

tert-Butyl (1R,2S,5S)-2-{{[3-(4-chlorophenyl)-3-hydroxypropanoyl]amino}-5-[(dimethylamino)carbonyl]}-cyclohexylcarbamate:



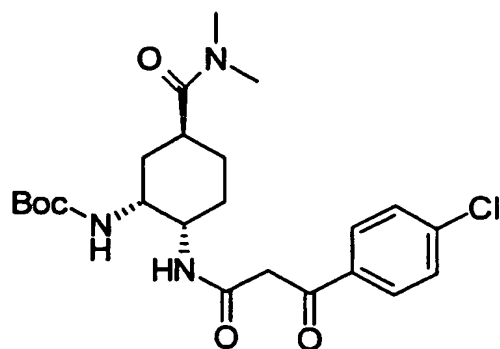
5 The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 381 in a similar manner to the process described in Referential Example 91.

¹H-NMR (CDCl₃) δ: 1.21-1.44 (2H,m), 1.46 (9H,s), 1.76-1.92 (2H,m), 1.95-2.10 (2H,m), 2.40-2.55 (2H,m), 2.55-2.68 (1H,m), 2.94 (3H,s), 3.05 (3H,s), 3.82-3.96 (1H,m), 4.02-4.17 (1H,m), 4.65-4.80 (2H,m), 5.03-5.13 (1H,m), 7.28-7.33 (5H,m).

MS (ESI) m/z: 468 (M+H)⁺.

15 [Referential Example 383]

tert-Butyl (1R,2S,5S)-2-{{[3-(4-chlorophenyl)-3-oxopropanoyl]amino}-5-[(dimethylamino)carbonyl]}-cyclohexylcarbamate:

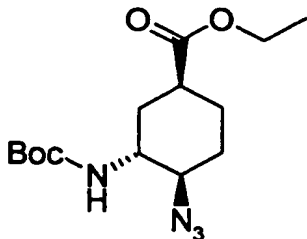


Manganese dioxide (0.47 g) was added to a solution of the compound (0.5 g) obtained in Referential Example 382 in 1,4-dioxane (20 ml) at room temperature, and the mixture was stirred for 4 days. Insoluble matter was removed by filtration through Celite pad, and the resultant filtrate was concentrated under reduced pressure to obtain the title compound (0.46 g).

¹H-NMR (DMSO-d₆) δ: 1.28-1.39(1H,m), 1.40(9H,s), 1.41-1.63(3H,m), 2.25-2.42(2H,m), 2.76(3H,s), 2.90-2.97(1H,m), 2.98(3H,s), 3.56(2H,s), 3.89-3.97(1H,m), 4.88-4.98(1H,m), 6.65-6.70(1H,m), 7.30-7.35(4H,m), 7.33(1H,dd,J=2.9,1.7Hz). MS (ESI,anion) m/z: 464(M-H)⁻.

[Referential Example 384]

15 Ethyl (1S,3R,4R)-4-azido-3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylate:



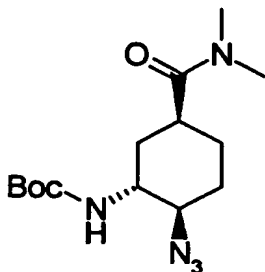
The title compound was obtained from the compound obtained in Referential Example 248 in a similar manner to the process described in Referential Example 249.

$[\alpha]_D^{25} +62^\circ$ (c=1, chloroform)

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.27(3H,t,J=7.1Hz), 1.46(9H,s), 1.61(1H,s), 1.61-1.71(2H,m), 1.81-1.90(1H,m), 1.97-2.03(1H,m), 2.22-2.28(1H,m), 2.56-2.60(1H,m), 3.54(1H,br.s), 3.63-3.68(1H,m), 4.16(2H,q,J=7.1Hz), 4.58(1H,br.s).

10 [Referential Example 385]

tert-Butyl (1R,2R,5S)-2-azido-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:



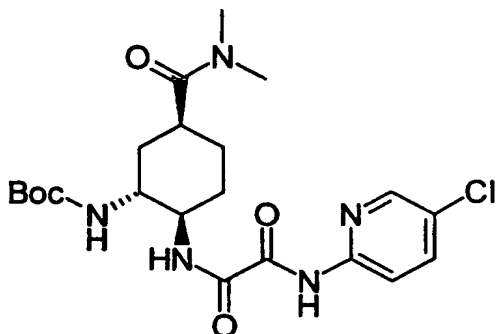
The title compound was obtained from the compound obtained in Referential Example 384 in similar manners to Referential Examples 250 and 251.

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.46(9H,s), 1.40-2.20(6H,m), 2.70-2.80(1H,m), 2.93(3H,s), 3.03(3H,s), 3.60-3.78(1H,m), 3.83-3.95(1H,m), 4.65(1H,d,J=7.2Hz).

20 [Referential Example 386]

tert-Butyl (1R,2R,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]cyclohexyl-

carbamate:



The title compound was obtained by converting the azide group of the compound obtained in Referential

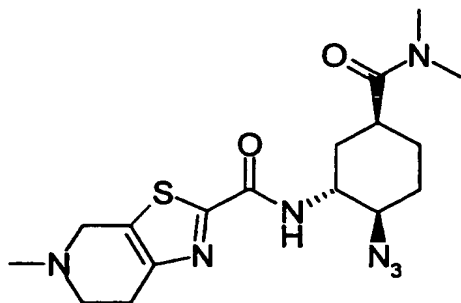
5 Example 385 into an amino group in a similar manner to the process described in Referential Example 90 and then condensing this product with the compound obtained in Referential Example 266 in a similar manner to the process described in Referential Example 91.

10 ¹H-NMR (CDCl₃) δ: 1.13-2.25(16H,m), 2.94(3H,s), 3.03(3H,s), 3.60-3.78(1H,m), 4.13-4.31(1H,m), 4.45-4.65(1H,m), 7.80(1H,dd,J=8.8,2.4Hz), 8.03(1H,br.s), 8.21(1H,d,J=8.8Hz), 8.29(1H,d,J=2.4Hz), 9.71(1H,s).

MS (ESI) m/z: 468(M+H)⁺.

15 [Referential Example 387]

N-{(1R,2R,5S)-2-Azido-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:



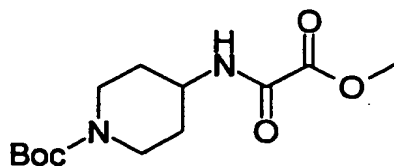
The title compound was obtained from the compound
 obtained in Referential Example 385 and the compound
 obtained in Referential Example 10 in a similar manner to
 5 the process described in Referential Example 252.

¹H-NMR (CDCl₃) δ: 1.75-2.08 (6H,m), 2.20-2.32 (1H,m),
 2.51 (3H,s), 2.75-2.97 (4H,m), 2.95 (3H,s), 3.04 (3H,s), 3.65-
 3.80 (3H,m), 4.27-4.39 (1H,m), 7.17-7.28 (1H,m).

MS (ESI) m/z: 392 (M+H)⁺.

10 [Referential Example 388]

tert-Butyl 4-[(2-methoxy-2-oxoacetyl)amino]piperidine-1-
 carboxylate:



The title compound was obtained from (4-amino-N-tert-
 15 butoxycarbonyl)piperidine and methyl chlorooxoacetate in a
 similar manner to the process described in Referential
 Example 242.

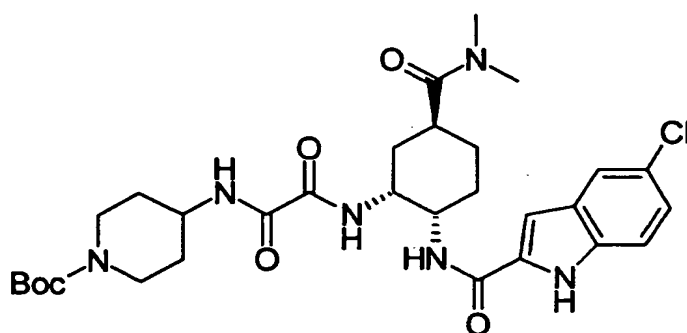
¹H-NMR (DMSO-d₆) δ: 1.46 (9H,s), 1.34-1.51 (2H,m), 1.89-

1.98 (2H,m), 2.82-2.96 (2H,m), 3.91 (3H,s), 3.88-4.14 (3H,m),
6.96-7.07 (1H,m).

MS (FAB) m/z: 287 (M+H)⁺.

[Referential Example 389]

- 5 tert-Butyl 4-{[2-({(1R,2S,5S)-2-{[(5-chloroindol-2-yl)-
carbonyl]amino}-5-[(dimethylamino)carboxyl]cyclohexyl)-
amino)-2-oxoacetyl]amino}piperidine-1-carboxylate:



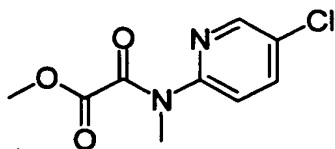
- The title compound was obtained from the compound
10 obtained in Referential Example 310 and the compound
obtained in Referential Example 388 in a similar manner to
the process described in Referential Example 191.

- ¹H-NMR (DMSO-d₆) δ: 1.46 (9H,s), 1.35-2.28 (11H,m), 2.70-
3.18 (9H,m), 3.80-4.57 (4H,m), 6.78 (1H,s), 7.15-8.12 (6H,m),
15 9.45 (1H,s).

MS (FAB) m/z: 617 (M+H)⁺.

[Referential Example 390]

Methyl 2-[(5-chloropyridin-2-yl)(methyl)amino]-2-
oxoacetate:



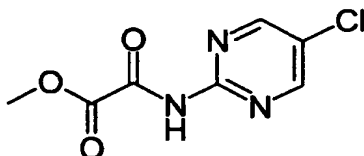
The title compound was obtained from 5-chloro-N-methyl-2-pyridineamine and methyl chlorooxoacetate in a similar manner to the process described in Referential
 5 Example 242.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.43(3H,s), 3.81(3H,s), 7.08(1H,br.s), 7.68-7.78(1H,m), 8.27(1H,br.s).

MS (ESI) m/z : 229($\text{M}+\text{H}$) $^+$.

[Referential Example 391]

10 Methyl 2-[(5-chloropyrimidin-2-yl)amino]-2-oxoacetate:



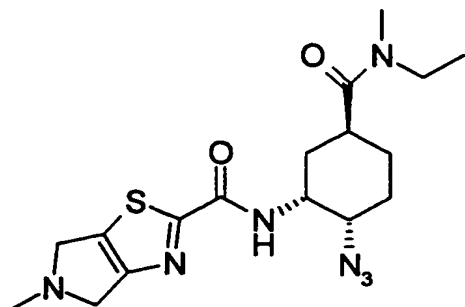
The title compound was obtained from 2-amino-5-chloropyrimidine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

15 $^1\text{H-NMR}$ (CDCl_3) δ : 4.00(3H,s), 8.63(2H,s), 9.58(1H,br.s).

MS (ESI) m/z : 215($\text{M}+\text{H}$) $^+$.

[Referential Example 392]

N-((1R,2S,5S)-2-Azido-5-{[ethyl(methyl)amino]carbonyl}-cyclohexyl)-5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]-
 20 thiazole-2-carboxamide:



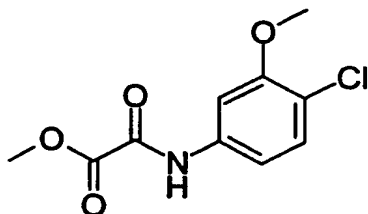
The title compound was obtained from the compound
 obtained in Referential Example 323 and the compound
 obtained in Referential Example 293 in a similar manner to
 5 the process described in Referential Example 252.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.08, 1.15 (3H, each t, $J=7.1\text{Hz}$), 1.74-
 1.88 (4H, m), 2.12-2.22 (2H, m), 2.67 (3H, s), 2.81-2.86 (1H, m),
 2.89, 2.96 (3H, each s), 3.28-3.43 (2H, m), 3.91-4.10 (5H, m),
 4.60-4.62 (1H, m), 7.21 (1H, d, $J=7.6\text{Hz}$).

10 MS (ESI) m/z : 392 ($\text{M}+\text{H}$) $^+$.

[Referential Example 393]

Methyl 2-(4-chloro-3-methoxyanilino)-2-oxoacetate:



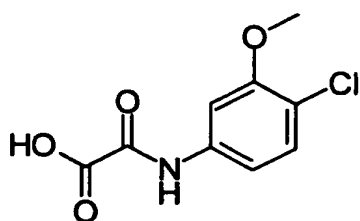
The title compound was obtained by reducing 2-chloro-
 15 5-nitroaniline in a similar manner to the process
 described in Referential Example 361 into an amino
 derivative and then condensing the amino derivative with

methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

¹H-NMR (CDCl₃) δ: 3.93(3H,s), 3.98(3H,s),
7.00(1H,dd,J=8.5,2.4Hz), 7.33(1H,d,J=8.5Hz),
5 7.57(1H,d,J=2.4Hz), 8.89(1H,br.s).

[Referential Example 394]

2-(4-Chloro-3-methoxyanilino)-2-oxoacetic acid:



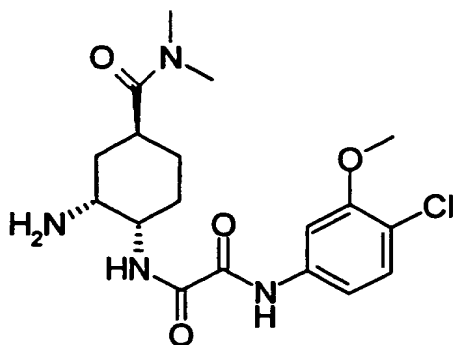
The title compound was obtained by hydrolyzing the
10 compound obtained in Referential Example 393 in a similar manner to the process described in Referential Example 359.

¹H-NMR (DMSO-d₆) δ: 3.81(3H,s), 7.36(1H,d,J=8.7Hz),
7.43(1H,d,J=8.7Hz), 7.65(1H,d,J=2.2Hz), 10.79(1H,s).

MS (ESI, anion) m/z: 228(M-H)⁻.

15 [Referential Example 395]

N¹-{(1S,2R,4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-N²-(4-chloro-3-methoxyphenyl)ethanediamide:

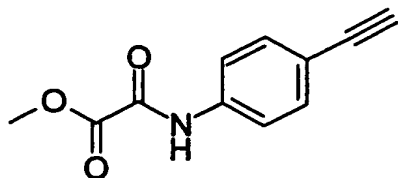


The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 394 in a similar manner to the process described in Referential Example 97, treating this product with hydrochloric acid in a similar manner to the process described in Referential Example 69 and then neutralizing it with a 1N aqueous solution of sodium hydroxide.

¹H-NMR (CDCl₃) δ: 1.48-2.00 (8H, m), 2.84-2.93 (1H, m), 2.95 (3H, s), 3.08 (3H, s), 3.33-3.35 (1H, m), 3.89-3.94 (4H, m), 7.06 (1H, dd, J=8.5, 2.2 Hz), 7.32 (1H, d, J=8.5 Hz), 7.56 (1H, d, J=2.2 Hz), 8.05 (1H, d, J=8.5 Hz), 9.43 (1H, br. s).
MS (ESI) m/z: 397 (M⁺).

[Referential Example 396]

Methyl 2-(4-ethynylanilino)-2-oxoacetate:



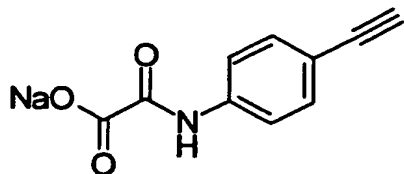
The title compound was obtained from 4-ethynylaniline

and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

$^1\text{H-NMR}$ (CDCl_3) δ : 3.09(1H,s), 3.98(3H,s), 7.50(2H,d,J=8.4Hz), 7.62(2H,d,J=8.4Hz), 8.89(1H,br.s).

5 [Referential Example 397]

Sodium 2-(4-ethynylanilino)-2-oxoacetate:

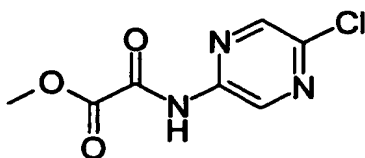


The title compound was obtained by hydrolyzing the compound obtained in Referential Example 396 with sodium hydroxide in a similar manner to the process described in Referential Example 266.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 4.06(1H,s), 7.39(2H,d,J=8.4Hz), 7.80(2H,d,J=8.4Hz), 10.33(1H,br.s).

[Referential Example 398]

15 Methyl 2-[(5-chloropyrazin-2-yl)amino]-2-oxoacetate:



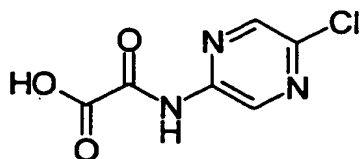
The title compound was obtained from 2-amino-5-chloropyrazine synthesized in accordance with literature (Sato, Nobuhiro et al., J. Heterocycl. Chem., 1982, 19(3), 673-4) and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.02 (3H, s), 8.35 (1H, d, $J=1.5\text{Hz}$),
9.37 (1H, d, $J=1.5\text{Hz}$), 9.41 (1H, br. s).

MS (FAB) m/z : 216 ($\text{M}+\text{H}$) $^+$.

[Referential Example 399]

5 2-[(5-Chloropyrazin-2-yl)amino]-2-oxoacetic acid:



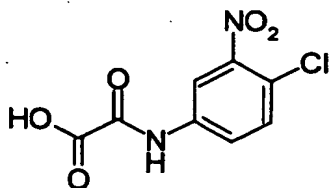
The title compound was obtained from the compound obtained in Referential Example 398 in a similar manner to the process described in Referential Example 359.

10 $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.62 (1H, s), 9.02 (1H, br. s), 11.30 (1H, s).

MS (EI) m/z : 201 M^+ .

[Referential Example 400]

2-(4-Chloro-3-nitroanilino)-2-oxoacetic acid:



15 The title compound was obtained by condensing 4-chloro-3-nitroaniline with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242 and then hydrolyzing this product in a similar manner to the process described in Referential Example 359.

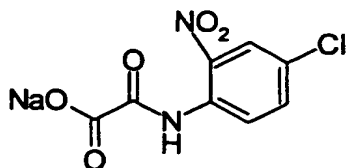
20 $^1\text{H-NMR}$ (DMSO-d_6) δ : 7.76 (1H, dd, $J=8.8\text{Hz}$),
8.04 (1H, dd, $J=8.8, 2.4\text{Hz}$), 8.55 (1H, d, $J=2.4\text{Hz}$), 11.24 (1H, s).

No proton attributable to the carboxylic acid was observed.

MS (EI) m/z: 244 M⁺.

[Referential Example 401]

Sodium 2-(4-chloro-2-nitroanilino)-2-oxoacetate:



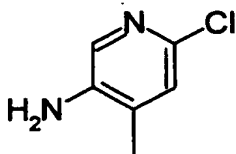
5

The title compound was obtained by condensing 4-chloro-2-nitroaniline with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242, hydrolyzing this product in a similar manner to the process described in Referential Example 266,
10 dissolving the resultant residue in methanol, adding a 1N aqueous solution of sodium hydroxide and collecting precipitate formed by filtration.

¹H-NMR (DMSO-d₆) δ: 7.84(1H,dd,J=9.0,2.5Hz),
15 8.20(1H,d,J=2.5Hz), 8.67(1H,d,J=9.0Hz), 11.89(1H,s).

[Referential Example 402]

6-Chloro-4-methyl-3-pyridineamine:



2-Chloro-4-methyl-5-nitropyridine (173 mg) was
20 dissolved in ethanol (5 ml), and a catalytic amount of Raney nickel catalyst was added to stir the mixture at

room temperature for 9 hours under a hydrogen atmosphere. The catalyst was removed by filtration, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel

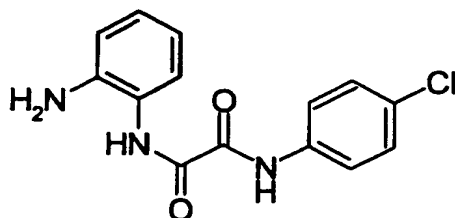
5 (hexane:ethyl acetate = 3:2) to obtain the title compound (113 mg).

$^1\text{H-NMR}$ (CDCl_3). δ : 2.13(3H,s), 3.85(2H,br.s), 6.96(1H,s), 7.74(1H,s).

MS (EI) m/z : 142 M^+ .

10 [Referential Example 403]

N^1 -(2-Aminophenyl)- N^2 -(4-chlorophenyl)ethanamide:



The title compound was obtained by condensing 1,2-benzenediamine with the compound obtained in Referential
15 Example 374 in a similar manner to the process described in Referential Example 59.

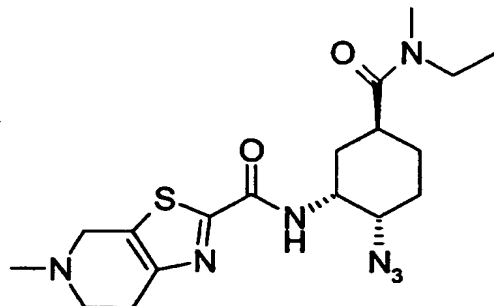
$^1\text{H-NMR}$ (DMSO-d_6) δ : 5.00(2H,s), 6.59-6.63(1H,m), 6.78(1H,dd, $J=8.1,1.2\text{Hz}$), 6.96-7.01(1H,m), 7.25(1H,dd, $J=7.8,1.2\text{Hz}$), 7.44(2H,d, $J=8.8\text{Hz}$),
20 7.91(2H,d, $J=8.8\text{Hz}$), 10.04(1H,s), 10.91(1H,s).

MS (FAB): 290($\text{M}+\text{H}$) $^+$.

[Referential Example 404]

$\text{N}-((1\text{R},2\text{S},5\text{S})-2\text{-Azido-5-}\{[\text{ethyl(methyl)amino}]\text{carbonyl}\})-$

cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:

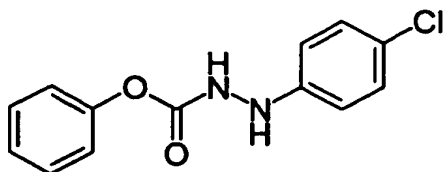


The title compound was obtained by treating the compound obtained in Referential Example 323 with hydrochloric acid, performing deprotection and then condensing this product with the compound obtained in Referential Example 10 in a similar manner to the process described in Referential Example 252.

¹H-NMR (CDCl₃) δ: 1.08 (1/2 of 3H, t, J=7.2Hz), 1.14 (1/2 of 3H, t, J=7.2Hz), 1.70-1.90 (4H, m), 2.10-2.25 (2H, m), 2.52 (3H, s), 2.78-3.00 (8H, m), 3.25-3.45 (2H, m), 3.69 (1H, d, J=13.4Hz), 3.73 (1H, d, J=13.4Hz), 3.87-3.95 (1H, m), 4.55-4.62 (1H, m), 7.26 (1H, d, J=7.6Hz).

[Referential Example 405]

Phenyl 2-(4-chlorophenyl)-1-hydrazinecarboxylate:



(4-Chlorophenyl)hydrazine hydrochloride (3.00 g) was dissolved in tetrahydrofuran (50 ml), diethyl ether (50

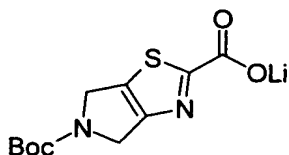
ml) and a saturated aqueous solution of sodium hydrogencarbonate. An organic layer was separated, dried over anhydrous sodium sulfate and then concentrated, giving (4-chlorophenyl)hydrazine as a brown solid. This product was dissolved in benzene (15 ml), and the solution was heated under reflux, to which a solution of diphenyl carbonate (5.22 g) in benzene (8.0 ml) was added dropwise over at least 30 minutes. After refluxing for 19 hours, the reaction mixture was allowed to cool and concentrated. Benzene (15 ml) was then added to the residue. The mixture was subjected to ultrasonic treatment, giving a suspension. After hexane (50 ml) was added to the suspension, and the mixture was stirred for 30 minutes, insoluble matter was collected by filtration and dried to obtain the title compound (1.05 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 5.86(1H,br.s), 6.83-6.92(3H,m), 7.17(1H,br.s), 7.20-7.32(4H,m), 7.37(2H,t, $J=7.7\text{Hz}$).

MS (ESI) m/z : 263($\text{M}+\text{H}$) $^+$.

[Referential Example 406]

Lithium 5-tert-butoxycarbonyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazole-2-carboxylate:

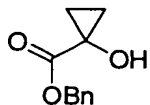


The title compound was obtained from the compound obtained in Referential Example 33 in a similar manner to the process described in Referential Example 10.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.46(9H,s), 4.30-4.70(4H,m).

[Referential Example 407]

Benzyl 1-hydroxycyclopropanecarboxylate:



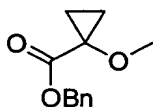
5 Triethylamine (1.0 ml) and benzyl bromide (650 μl) were added to a solution of 1-hydroxycyclopropane-carboxylic acid (409 mg) in tetrahydrofuran (3.0 ml), and the mixture was stirred at room temperature for 23 hours. Methylene chloride and 1N hydrochloric acid were added to
10 the reaction mixture to separate the mixture into two layers. An organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. A crude product was purified by
15 column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (607 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.16(2H,dd, $J=7.9,4.9\text{Hz}$), 1.32(2H,dd, $J=7.9,4.9\text{Hz}$), 3.09(0.5H,s), 3.11(0.5H,s), 5.17(2H,s), 7.30-7.39(5H,m).

20 MS (FAB) m/z : 192($\text{M}+\text{H}$) $^+$.

[Referential Example 408]

Benzyl 1-methoxycyclopropanecarboxylate:



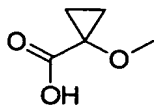
60% Sodium hydride in oil (345 mg) and methyl iodide (900 μ l) were added to a solution of the compound (600 mg) obtained in Referential Example 407 in tetrahydrofuran (5.0 ml), and the mixture was heated under reflux for 28 hours. Ethyl acetate and a saturated aqueous solution of ammonium chloride were added to the reaction mixture to separate the mixture into two layers. An organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. A crude product was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1) to obtain the title compound (340 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.16(2H,dd,J=7.9,4.8Hz), 1.31(2H,dd,J=7.9,4.8Hz), 3.42(3H,s), 5.18(2H,s), 7.30-7.39(5H,m).

MS (FAB) m/z : 207(M+H) $^+$.

[Referential Example 409]

1-Methoxycyclopropanecarboxylic acid:

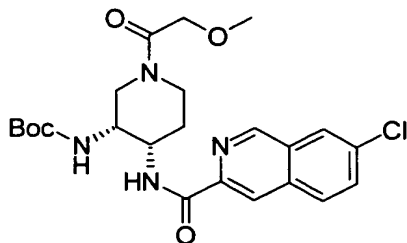


The title compound was obtained from the compound obtained in Referential Example 408 in a similar manner to the process described in Referential Example 152.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.23(2H,dd,J=8.0,4.9Hz), 1.38(2H,dd,J=8.0,4.9Hz), 3.45(3H,s), 8.80-9.00(1H,br).

[Referential Example 410]

tert-Butyl (3R,4S)-4-({7-chloroisoquinolin-3-yl}carbonyl)-
amino)-1-(2-methoxyacetyl)piperidin-3-ylcarbamate:



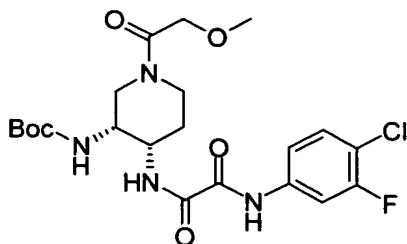
The title compound was obtained from the compound
5 obtained in Referential Example 220 in a similar manner to
the process described in Referential Example 214.

¹H-NMR (CDCl₃) δ: 1.46(9H,br s), 1.62-1.80(1H,m), 2.04-
2.22(1H,m), 2.95-3.32(1H,m), 3.38-3.53(1H,m), 3.46(3H,s),
3.84-3.95(1H,m), 4.02-4.27(3H,m), 4.30-4.65(2H,m), 4.87-
10 4.98(0.5H,br), 5.32-5.43(0.5H,br), 7.71(1H,dd,J=8.8,2.0Hz),
7.94(1H,d,J=8.8Hz), 8.02(1H,s), 8.55-8.66(0.7H,br),
8.58(1H,s), 8.73-8.85(0.3H,br), 9.14(1H,br s).

MS (ESI) m/z: 477(M+H)⁺.

[Referential Example 411]

15 tert-Butyl (3R,4S)-4-{[2-(4-chloro-3-fluoroanilino)-2-
oxoacetyl]amino)-1-(2-methoxyacetyl)piperidin-3-yl-
carbamate:



The title compound was obtained by condensing the

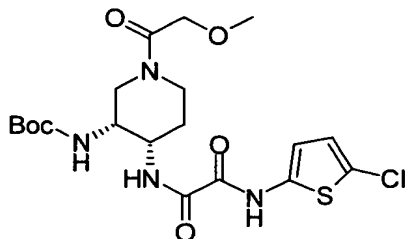
compound obtained in Referential Example 220 with the compound obtained in Referential Example 337 in a similar manner to the process described in Referential Example 214.

¹H-NMR (CDCl₃) δ: 1.46(9H,s), 1.60-1.75(1H,m), 1.92-
5 2.08(1H,m), 2.68-2.80(0.5H,m), 2.88-3.03(0.5H,m), 3.06-
3.24(0.5H,m), 3.27-3.36(0.5H,m), 3.45(3H,s), 3.90-
4.22(5H,m), 4.56-4.71(1H,m), 4.80-4.92(0.3H,br), 5.44-
5.54(0.7H,br), 7.24(1H,d,J=12.9Hz), 7.35(1H,t,J=8.3Hz),
7.72(1H,dd,J=8.3,2.3Hz), 8.20-8.42(1H,br), 9.18-
10 9.28(1H,br).

MS (ESI) m/z: 487(M+H)⁺.

[Referential Example 412]

tert-Butyl (3R,4S)-4-({2-[(5-chloro-2-thienyl)amino]-2-
oxoacetyl}amino)-1-(2-methoxyacetyl)piperidin-3-yl-
15 carbamate:



The title compound was obtained from the compound obtained in Referential Example 220 and the lithium salt of a carboxylic acid obtained by hydrolyzing the compound obtained in Referential Example 356 in a similar manner to the process described in Referential Example 214.

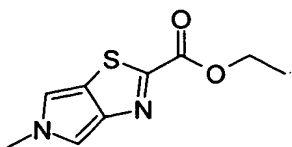
¹H-NMR (CDCl₃) δ: 1.45(9H,s), 1.55-1.75(1H,br), 1.90-
2.10(1H,br), 2.68-2.80(0.7H,m), 2.90-3.03(0.3H,br), 3.07-

3.22 (0.3H, br), 3.25-3.35 (0.7H, br), 3.45 (3H, s), 3.83-4.22 (5H, m), 4.55-4.70 (1H, br), 4.80-4.90 (0.2H, br), 5.07-5.14 (0.2H, br), 5.44-5.55 (0.6H, br), 6.58-6.64 (1H, br), 6.73 (1H, d, J=3.9Hz), 8.05-8.27 (1H, br), 9.65-9.88 (1H, br).

5 MS (FAB) m/z: 475 (M+H)⁺.

[Referential Example 413]

Ethyl 5-methyl-5H-pyrrolo[3,4-d]thiazolo-2-carboxylate:



1) Ethyl 2-thioxoacetate (26.75 g) was added to a
10 solution of 3-bromo-2-butanone (26.36 g) in ethanol (250 ml), and the mixture was heated under reflux for 14 hours. After cooling the reaction mixture, it was concentrated, and ethyl acetate and saturated aqueous solution of sodium chloride were added to separate the mixture into two
15 layers. An organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by
20 column chromatography on silica gel (hexane:ethyl acetate = 6:1) to obtain ethyl 4,5-dimethylthiazole-2-carboxylate (19.53 g).

¹H-NMR (CDCl₃) δ: 1.42 (3H, t, J=7.1Hz), 2.42 (3H, s), 2.44 (3H, s), 4.45 (2H, q, J=7.1Hz).

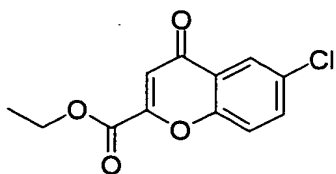
25 2) N-Bromosuccinimide (62.42 g) and 2,2'-azobis-

isobutyronitrile (227 mg) were added to a solution of the above-described product (19.53 g) in 1,2-dichloroethane (500 ml), and the mixture was refluxed for 42 hours. After cooling the reaction mixture, water and methylene chloride were added to separate the mixture into two layers. An organic layer was washed with saturated aqueous solution of sodium chloride and then concentrated under reduced pressure to obtain a crude product (40.54 g) as a dark brown oil. Triethylamine (8.0 ml) and a 2 M tetrahydrofuran solution (11.0 ml) of methylamine were added to the crude product (8.41 g), and the mixture was stirred at room temperature for 3 days. After the reaction mixture was concentrated under reduced pressure, methylene chloride and saturated aqueous solution of sodium chloride were added to the residue to separate the mixture into two layers. An organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (270 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.45(3H,t,J=7.1Hz), 3.91(3H,s), 4.48(2H,q,J=7.1Hz), 6.73(1H,d,J=1.7Hz), 7.30(1H,d,J=1.7Hz).
MS (ESI) m/z : 211(M+H) $^+$.

[Referential Example 414]

Ethyl 6-chloro-4-oxo-4H-chromene-2-carboxylate:



About 60% sodium hydride in oil (1.68 g) was added to ethanol (10 ml) under purging with argon, and the mixture was stirred at room temperature for 10 minutes. After
 5 diethyl oxalate (3.36 ml) was added, an ethanol solution (20 ml) of 5'-chloro-2'-hydroxyacetophenone (2.82 g) was added dropwise. Ethanol (40 ml) was additionally added, and the mixture was refluxed for 1.5 hours and stirred at 50°C for 14 hours. Concentrated sulfuric acid (1.5 ml) and
 10 ethanol (10 ml) were added to the reaction mixture, and the resultant mixture was refluxed for 4 hours. After cooling, the solvent was decreased to a half by concentration under reduced pressure. Toluene and a 1N aqueous solution (15 ml) of sodium hydroxide were added to
 15 the concentrated the reaction mixture. Extraction was conducted with ethyl acetate, and the resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure,
 20 and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 7:1), the resultant solids were washed with hexane to obtain the title compound (1.20 g).

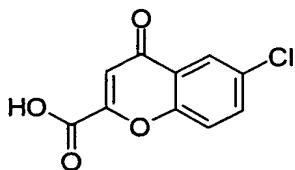
¹H-NMR (CDCl₃) δ: 1.44 (3H, t, J=7.1Hz), 4.47 (2H, q, J=7.1Hz),
 25 7.12 (1H, s), 7.58 (1H, d, J=9.0Hz), 7.69 (1H, dd, J=9.0, 2.7Hz),

8.16(1H,d,J=2.7Hz).

MS (ESI) m/z: 293(M+MeCN+H)⁺.

[Referential Example 415]

6-Chloro-4-oxo-4H-chromene-2-carboxylic acid:



5

The title compound was obtained from the compound obtained in Referential Example 414 in a similar manner to the process described in Referential Example 359.

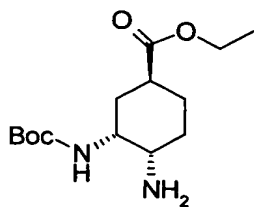
¹H-NMR (CDCl₃) δ: 7.12(1H,s), 7.60(1H,d,J=8.8Hz),

10 7.69(1H,dd,J=8.8,2.7Hz), 8.15(1H,d,J=2.7Hz).

MS (FAB) m/z: 225(M+H)⁺.

[Referential Example 416]

Ethyl (1S,3R,4S)-4-amino-3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylate:



15

The title compound was obtained from the compound obtained in Referential Example 249 in a similar manner to the process described in Referential Example 90.

¹H-NMR (CDCl₃) δ: 1.20-1.80(4H,m), 1.25(3H,t,J=7.3Hz),

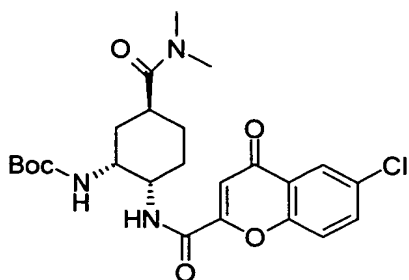
20 1.46(9H,s), 1.85-2.00(1H,m), 2.10-2.20(1H,m), 2.30-

2.45(1H,m), 2.90-3.00(1H,m), 3.84(1H,br s),

4.12(2H,q,J=7.3Hz), 4.75(1H,br s).

[Referential Example 417]

tert-Butyl (1R,2S,5S)-2-{{(6-chloro-4-oxo-4H-chromen-2-yl)carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl-carbamate:



5

N,N-Dimethylformamide (0.02 ml) was added to a solution of the compound (213 mg) obtained in Referential Example 415 in thionyl chloride (2.0 ml), and the mixture was refluxed for 15 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (4.0 ml). To the solution were added triethylamine (500 μ l) and the compound (294 mg) obtained in Referential Example 144, and the mixture was stirred at room temperature for 15 minutes. Ethyl acetate and a 10% aqueous solution of citric acid to separate the reaction mixture into two layers. An organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 30:1) to obtain the title compound (230 mg).

10

15

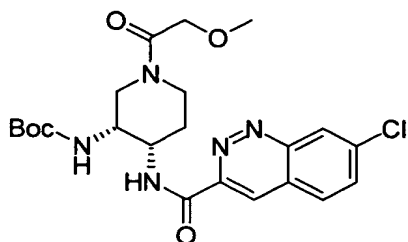
20

¹H-NMR (CDCl₃) δ: 1.33-1.77(3H,m), 1.50(9H,s), 1.81-
2.34(3H,m), 2.63-2.80(1H,m), 2.95(3H,s), 3.10(3H,s), 3.90-
4.04(1H,br), 4.18-4.31(1H,br), 4.93-5.12(1H,br),
7.13(1H,s), 7.55(1H,d,J=8.8Hz), 7.66(1H,dd,J=8.8,2.4Hz),
5 8.14(1H,d,J=2.4Hz), 8.77-8.92(1H,br).

MS (ESI) m/z: 492(M+H)⁺.

[Referential Example 418]

tert-Butyl (3R,4S)-4-{[(7-chlorocinnolin-3-
yl)carbonyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl-
10 carbamate:



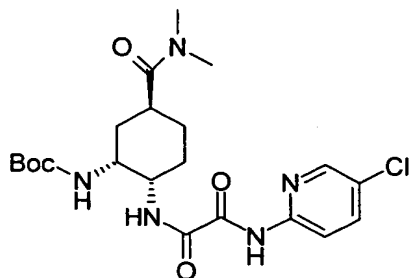
The title compound was obtained from the compound
obtained in Referential Example 220 and the lithium salt
of a carboxylic acid obtained by hydrolyzing the ester
15 described in Referential Example 297 in a similar manner
to the process described in Referential Example 214.

¹H-NMR (CDCl₃) δ: 1.38(9H,s), 1.65-1.90(1H,m), 1.90-
2.15(1H,m), 2.80-3.00(0.6H,m), 3.00-3.15(0.4H,m), 3.20-
3.50(1H,m), 3.46(3H,s), 3.80-4.70(6H,m), 4.87(0.4H,br s),
20 5.30(0.6H,br s), 7.78(1H,d,J=8.8Hz), 7.97(1H,d,J=8.8Hz),
8.61(1H,s), 8.62-8.90(1H,br), 8.73(1H,s).

MS (ESI) m/z: 478(M+H)⁺.

[Referential Example 419]

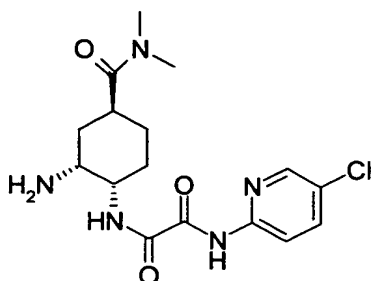
tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]cyclohexyl-carbamate:



- 5 The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 266 in a similar manner to the process described in Referential Example 68.
- ¹H-NMR (CDCl₃) δ: 1.35-1.65(1H,m), 1.45(9H,s), 1.65-1.89(2H,m), 1.90-2.10(3H,m), 2.56-2.74(1H,br), 2.95(3H,s), 3.06(3H,s), 3.94-4.01(1H,m), 4.18-4.27(1H,m), 4.70-4.90(0.7H,br), 5.80-6.20(0.3H,br), 7.68(1H,dd,J=8.9,2.6Hz), 7.83(1H,br s), 8.14(1H,br d,J=7.8Hz), 8.30(1H,s), 9.72(1H,s).
- 10
- 15 MS (ESI) m/z: 468(M+H)⁺.

[Referential Example 420]

N¹-{(1S,2R,4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-N²-(5-chloropyridin-2-yl)ethanediamide hydrochloride:



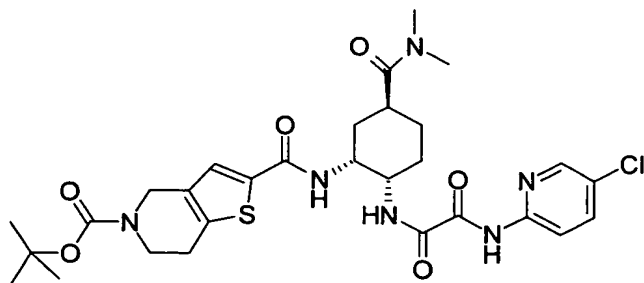
The title compound was obtained from the compound obtained in Referential Example 419 in a similar manner to the process described in Referential Example 69.

¹H-NMR (DMSO-d₆) δ: 1.38-1.51(1H,m), 1.65-1.85(3H,m), 1.96-2.10(2H, m), 2.81(3H,s), 3.07(3H,s), 3.23-3.33(1H,m), 3.74(1H,br s), 3.84-3.92(1H,m), 8.02(1H,dd,J=9.0,2.5Hz), 8.07(1H,d,J=9.0Hz), 8.34(3H,br s), 8.46(1H,d,J=2.5Hz), 8.96(1H,d,J=6.6Hz), 10.34(1H,s).

MS (ESI) m/z: 368 (M+H)⁺.

[Referential Example 421]

tert-Butyl 2-[(1R,2S,5S)-2-[(2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl)amino]-5-[(dimethylamino)carbonyl]-cyclohexyl)amino)carbonyl]-6,7-dihydrothieno[3,2-c]-pyridine-5(4H)-carboxylate:



The title compound was obtained by condensing the compound obtained in Referential Example 420 with 5-(tert-

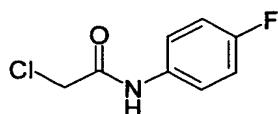
butoxycarbonyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50(9H,s), 1.73-1.95(3H,m), 1.95-2.06(1H,m), 2.08-2.20(2H,m), 2.82(3H,br s), 2.94(3H,s),
5 3.03(3H,s), 3.60-3.80(2H,m), 3.96-4.08(1H,m),
4.44(2H,br s), 4.66(1H,br s), 6.74(1H,br s), 7.20-7.32(1H,m), 7.66(1H,dd, $J=9.0, 2.4\text{Hz}$), 8.13(1H,d, $J=9.0\text{Hz}$),
8.13-8.25(1H,m), 8.28(1H,d, $J=2.4\text{Hz}$), 9.75(1H,s).

MS (ESI) m/z : 633($\text{M}+\text{H}$) $^+$.

10 [Referential Example 422]

2-Chloro-N-(4-fluorophenyl)acetamide:



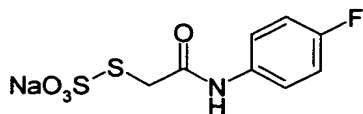
The title compound was obtained from p-fluoroaniline in a similar manner to the process described in

15 Referential Example 350.

$^1\text{H-NMR}$ (CDCl_3) δ : 4.19(2H,s), 7.05(2H,t, $J=8.6\text{Hz}$),
7.51(2H,dd, $J=9.1, 4.7\text{Hz}$), 8.19(1H,br s).

[Referential Example 423]

Sodium S-[2-(4-fluoroanilino)-2-oxoethyl]thiosulfate:



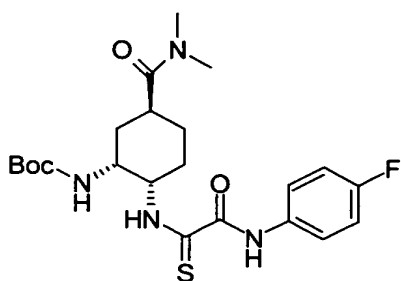
20

The title compound was obtained from the compound obtained in Referential Example 422 in a similar manner to the process described in Referential Example 351.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.72 (2H, s), 7.14 (2H, t, $J=9.0\text{Hz}$),
7.56 (2H, dd, $J=9.0, 5.1\text{Hz}$), 10.21 (1H, s).

[Referential Example 424]

tert-Butyl (1R,2S,5S)-5-[(dimethylamino)carbonyl]-2-[[2-(4-fluoroanilino)-2-oxoethanethioyl]amino]cyclohexyl-
5 carbamate:



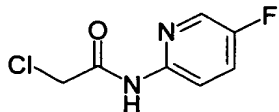
The compound (1.1 g) obtained in Referential Example
144 and the compound (1.2 g) obtained in Referential
10 Example 423 were dissolved in N-methylmorpholine (20 ml),
and the temperature of a bath was raised from room
temperature to 140°C over 15 minutes to heat and stir the
mixture for 15 minutes at the same temperature. After
allowing to cool, ice water was added to the reaction
15 mixture to collect insoluble matter by filtration. This
product was purified by column chromatography on silica
gel (methylene chloride:methanol = 200:1 \rightarrow 197:3) to
obtain the title compound (1.43 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (9H, s), 1.70-2.10 (5H, m), 2.10-
20 2.30 (1H, m), 2.60-2.80 (1H, m), 2.96 (3H, s), 3.07 (3H, s), 4.30-
4.50 (2H, m), 4.65-4.85 (1H, m), 7.06 (2H, t, $J=8.5\text{Hz}$), 7.50-
7.70 (2H, m), 9.75-9.95 (1H, m), 10.13 (1H, s).

MS (ESI) m/z : 467 ($\text{M}+\text{H}$) $^+$.

[Referential Example 425]

2-Chloro-N-(5-fluoropyridin-2-yl)acetamide hydrochloride:



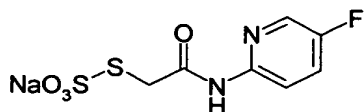
The title compound was obtained from 2-amino-5-
5 fluoropyridine in a similar manner to the process
described in Referential Example 352.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 4.35 (2H, s), 7.74-7.82 (1H, m),
8.10 (1H, dd, $J=9.0, 4.2\text{Hz}$), 8.36 (1H, d, $J=2.9\text{Hz}$), (1H, br s).

MS (ESI) m/z : 188 ($M+H$) $^+$.

10 [Referential Example 426]

Sodium S-{2-[(5-fluoropyridin-2-yl)amino]-2-
oxoethyl}thiosulfate:

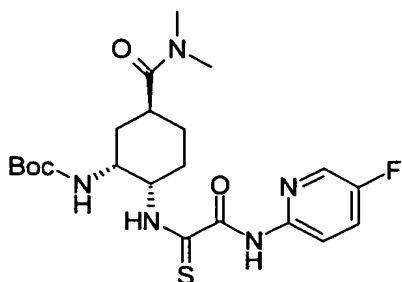


The title compound was obtained from the compound
15 obtained in Referential Example 425 in a similar manner to
the process described in Referential Example 353.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 3.75 (2H, s), 7.67-7.77 (1H, m),
8.07 (1H, dd, $J=9.2, 4.2\text{Hz}$), 8.28 (1H, d, $J=2.9\text{Hz}$), 10.48 (1H, s).

[Referential Example 427]

20 tert-Butyl (1R,2S,5S)-5-[(dimethylamino)carbonyl]-2-({2-
[(5-fluoropyridin-2-yl)amino]-2-oxoethanethioyl}amino)-
cyclohexylcarbamate:



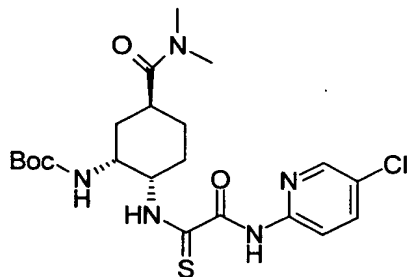
A solution of the compound (1.20 g) obtained in Referential Example 144 in pyridine (70 ml) was heated to 120°C, and the compound (2.42 g) obtained in Referential Example 426 was added. After stirring the mixture for 30 minutes, the reaction mixture was allowed to cool to room temperature, and the solvent was distilled off under reduced pressure. Methylene chloride (100 ml), a saturated aqueous solution (100 ml) of sodium hydrogencarbonate and water (50 ml) were added to the resultant residue to conduct liquid separation. A water layer was then extracted with methylene chloride. Organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (hexane:tetrahydrofuran = 1:1). After the resultant solids were slurried for 1 hour in isopropyl ether (40 ml), they were collected by filtration and dried to obtain the title compound (920 mg).

¹H-NMR (CDCl₃) δ: 1.47(9H,s), 1.70-2.10(5H,m), 2.27(1H,br s), 2.70(1H,br s), 2.96(3H,s), 3.08(3H,s), 4.34-4.44(2H,m), 4.77(1H,br s), 7.44-7.51(1H,m), 8.18-8.27(2H,m), 9.90(1H,br s), 10.57(1H,s).

MS (ESI) m/z : 468 ($M+H$)⁺.

[Referential Example 428]

tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-
2-oxoethanethioyl}amino)-5-[(dimethylamino)carbonyl]-
5 cyclohexylcarbamate:

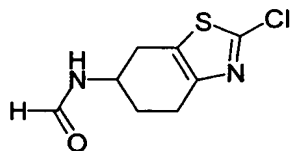


The title compound was obtained from the compound
obtained in Referential Example 144 and the compound
obtained in Referential Example 353 in a similar manner to
the process described in Referential Example 427.

¹H-NMR (CDCl₃) δ : 1.43 (9H, s), 1.65-2.35 (6H, m),
2.70 (1H, br s), 2.95 (3H, s), 3.09 (3H, s), 4.30-4.60 (2H, m),
4.87 (1/2H, br s), 6.92 (1/2H, br s), 7.69 (1H, dd, $J=8.9, 2.6$ Hz),
7.95-8.20 (1H, br), 8.29 (1H, s), 9.67 (1/2H, br s),
9.93 (1/2H, br s), 10.54 (1H, br s).

[Referential Example 429]

2-Chloro-4,5,6,7-tetrahydrobenzothiazol-6-ylformamide:



Ammonium acetate (18.58 g) and sodium
cyanoborohydride (10.68 g) were added to a solution of 2-
chloro-5-oxo-4,5,6,7-tetrahydrobenzo[d]thiazole (Helv. Cim.

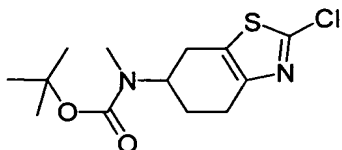
Acta., 1994, Vol. 77, p. 1256) (4.53 g) in methanol (200 ml), and the mixture was heated under reflux. After 19 hours, hydrochloric acid was added to decompose excessive reagents before the reaction mixture was concentrated under reduced pressure. After the residue was alkalified with a 1N aqueous solution of sodium hydroxide, methylene chloride was added to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was subjected to column chromatography on silica gel (methylene chloride:methanol = 20:1), and the solvent was distilled off to obtain a pale yellow oil (2.42 g). This oil was dissolved in methylene chloride (100 ml), and formic acid (530 μ l), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.68 g), 1-hydroxybenzotriazole (2.60 g) and N-methylmorpholine (3.88 g) were added to stir the mixture at room temperature. After 20 hours, methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the reaction mixture to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, the solvent was then distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1) to obtain the title compound (2.21 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.93-2.11(2H,m), 2.63-2.69(1H,m), 2.83-

2.89 (2H, m), 3.13 (1H, dd, J=16.2, 4.4 Hz), 4.46-4.48 (1H, m),
5.76 (1H, br s), 8.17 (1H, s).

[Referential Example 430]

tert-Butyl N-(2-chloro-4,5,6,7-tetrahydrobenzothiazol-6-
5 yl)-N-methylcarbamate:



A 1 M tetrahydrofuran solution (14.6 ml) of borane-tetrahydrofuran complex was added to a solution of the compound (2.11 g) obtained in Referential Example 429 in
10 tetrahydrofuran (50 ml), and the mixture was heated under reflux. After 15 hours, a 1 M tetrahydrofuran solution (6.0 ml) of borane-tetrahydrofuran complex was additionally added to heat the mixture under reflux. After
4 hours, ethanol (10 ml) and 1N hydrochloric acid (15 ml)
15 were added to heat the mixture under reflux. After 3 hours, the reaction mixture was concentrated under reduced pressure. A 1N aqueous solution of sodium hydroxide and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was dried
20 over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was dissolved in methylene chloride (50 ml), and triethylamine (1.28 g) and di-tert-butyl dicarbonate (2.21 g) were added to stir the mixture at room temperature.
25 After 30 minutes, methylene chloride and 1N hydrochloric

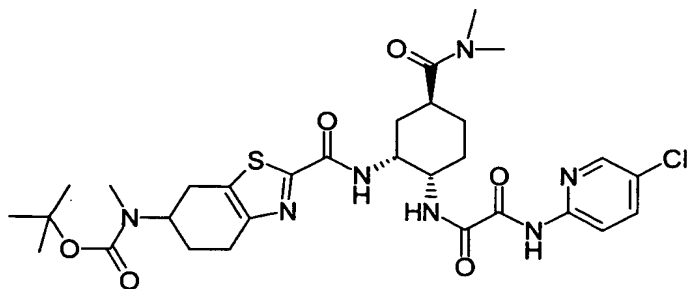
acid were added to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1) to obtain the title compound (2.26 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.47(9H,s), 1.96-1.98(2H,m), 2.80-2.96(7H,m), 4.40-4.50(1H,m).

MS (FAB) m/z : 303($\text{M}+\text{H}$) $^+$.

10 [Referential Example 431]

tert-Butyl N-(2-[(1R,2S,5S)-2-[(2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl)amino]-5-[(dimethylamino)carbonyl]-cyclohexyl)amino)carbonyl]-4,5,6,7-tetrahydrobenzothiazol-6-yl)-N-methylcarbamate:



15

After a solution of the compound (1.0 g) obtained in Referential Example 430 in diethyl ether (10 ml)-tetrahydrofuran (5 ml) was cooled -78°C , a 1.6N pentane solution (3.1 ml) of tert-butyllithium was added, and the mixture was stirred for 20 minutes. Carbon dioxide was then introduced for 20 minutes. The reaction mixture was warmed to room temperature and concentrated under reduced

pressure, giving lithium 6-[(tert-butoxycarbonyl)(methyl)-amino]-4,5,6,7-tetrahydrobenzothiazole-2-carboxylate.

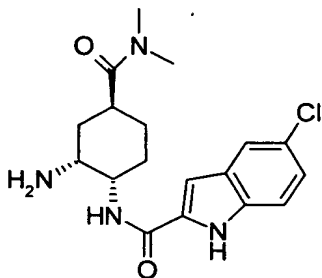
The lithium salt (350.2 mg) of the carboxylic acid obtained by the above-described reaction, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (287.6 mg), 1-hydroxybenzotriazole (202.7 mg) and N-methylmorpholine (0.319 ml) were added to a solution of the compound (490.5 mg) obtained in Referential Example 420 in N,N-dimethylformamide (20 ml), and the mixture was stirred at room temperature for 4 days. The solvent was distilled off under reduced pressure, and water and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was then successively washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel (methylene chloride:methanol = 40:1 → 20:1) to obtain the title compound (323.9 mg).

¹H-NMR (CDCl₃) δ: 1.48, 1.49 (total 9H, each s), 1.60-1.92 (4H, m), 1.95-2.20 (6H, m), 2.78-3.10 (3H, m), 2.83 (3H, s), 2.95 (3H, s), 3.06, 3.07 (total 3H, each s), 4.05-4.15 (1H, m), 4.20-4.60 (1H, m), 4.63-4.73 (1H, m), 7.39 (1H, d, J=8.6 Hz), 7.68 (1H, dt, J=8.8, 2.6 Hz), 7.95-8.10 (1H, m), 8.13-8.22 (1H, m), 8.30-8.35 (1H, m), 9.72 (1H, brs).

MS (ESI) m/z: 662 (M+H)⁺.

[Referential Example 432]

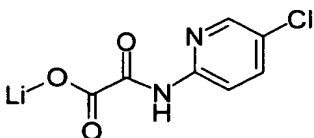
N-((1S,2R,4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl)-5-chloroindole-2-carboxamide hydrochloride:



5 The title compound was obtained by deprotecting the compound obtained in Referential Example 310 in a similar manner to the process described in Referential Example 69. ¹H-NMR (DMSO-d₆) δ: 1.43-1.56(0.5H,m), 1.72-1.97(4.5H,m), 2.82(3H,s), 3.06(3H,s), 3.11-3.26(1H,m), 3.75-3.84(1H,m), 10 4.07-4.14(1H,m), 4.22-4.41(1H,m), 7.19(1H,dd,J=2.0,8.8Hz), 7.29(1H,d,J=2.0Hz), 7.45(1H,d,J=8.8Hz), 7.72(1H,s), 8.07(3H,br), 8.47(1H,m), 11.85(1H,br).

[Referential Example 433]

Lithium 2-[(5-chloropyridin-2-yl)amino]-2-oxoacetate:



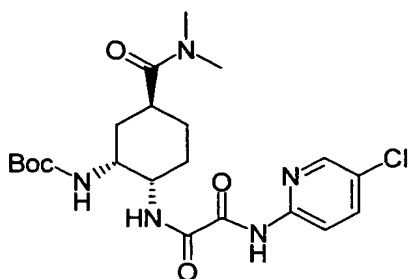
15 Methyl chlorooxoacetate (78.7 ml) was added dropwise to a suspension of 2-amino-5-chloropyridine (100 g) and sodium hydrogencarbonate (78.4 g) in tetrahydrofuran (2000 ml) at 0°C, and the mixture was stirred at room 20 temperature for 2 hours. After the reaction mixture was added to a mixture of diethyl ether (2000 ml), ammonium

chloride (62.4 g) and water (1000 ml), liquid separation was performed. The resultant water layer was extracted with methylene chloride. Organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was
5 distilled off under reduced pressure to obtain methyl 2-[(5-chloropyridin-2-yl)amino]-2-oxoacetate (162 g). Water (450 ml) and lithium hydroxide (18.2 g) were added to a solution of this ester (160 g) in tetrahydrofuran (1800 ml). After the mixture was stirred at room temperature for
10 2 hours, the solvent was distilled off under reduced pressure, and hexane (3000 ml) was added to the resultant residue to stir the mixture for 3 hours. Solids were collected by filtration and dried. Acetonitrile (1000 ml) was added to the solids (190 g), and the mixture was
15 stirred for 1 hour. Solids formed were collected by filtration, washed with diethyl ether (500 ml) and then dried to obtain the title compound (158 g).

¹H-NMR (DMSO-d₆) δ: 7.92(1H,dd,J=9.1,2.7Hz),
8.13(1H,dd,J=9.1,0.5Hz), 8.36(1H,dd,J=2.7,0.5Hz),
20 10.19(1H,s).

[Referential Example 434]

tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]cyclohexyl-carbamate:



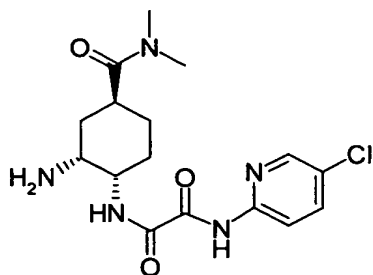
The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 433 in a similar manner to
 5 Referential Example 91.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.25-1.55 (1H, m), 1.45 (9H, s), 1.60-2.15 (5H, m), 2.56-2.74 (1H, br), 2.95 (3H, s), 3.06 (3H, s), 3.90-4.01 (1H, m), 4.18-4.27 (1H, m), 4.70-4.85 (0.7H, br), 5.70-6.00 (0.3H, br), 7.70 (1H, dd, $J=8.8, 2.4\text{Hz}$), 7.75-8.00 (1H, br), 8.16 (1H, br d, $J=8.8\text{Hz}$), 8.30 (1H, d, $J=2.4\text{Hz}$), 9.73 (1H, s).

MS (ESI) m/z : 468 ($\text{M}+\text{H}$) $^+$.

[Referential Example 435]

N^1 -{(1S, 2R, 4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl}- N^2 -(5-chloropyridin-2-yl)ethanediamide hydrochloride:
 15



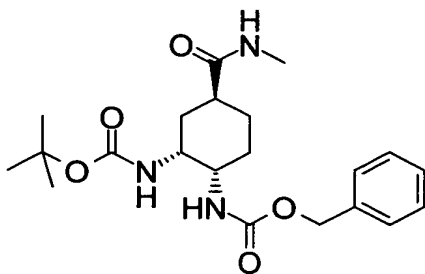
The title compound was obtained from the compound obtained in Referential Example 434 in a similar manner to

Referential Example 69.

¹H-NMR (DMSO-d₆) δ: 1.38-1.51(1H,m), 1.65-1.85(3H,m), 1.92-2.09(2H,m), 2.80(3H,s), 3.06(3H,s), 3.20-3.32(1H,m), 3.55-4.40(2H,br), 8.02(1H,dd,J=9.1,2.5Hz), 8.07(1H,d,J=9.1Hz),
5 8.15-8.40(3H,br), 8.45(1H,d,J=2.5Hz), 8.96(1H,d,J=6.6Hz), 10.33(1H,s).

[Referential Example 436]

Benzyl (1S,2R,4S)-2-[(tert-butoxycarbonyl)amino]-4-[(methylamino)carbonyl]cyclohexylcarbamate:



10

The title compound was obtained from the compound obtained in Referential Example 142 and methylamine hydrochloride in a similar manner to Referential Example 143.

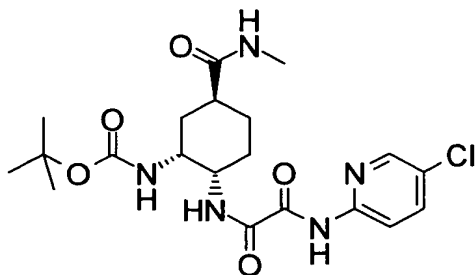
15 ¹H-NMR (DMSO-d₆) δ: 1.39(9H,s), 1.40-1.61(4H,m), 1.63-1.73(1H,m), 1.75-1.85(1H,m), 2.23-2.48(1H,m), 2.53(3H,d,J=4.6Hz), 3.48(1H,br.s), 3.80-3.91(1H,m), 5.01(1H,1/2ABq,J=12.1Hz), 5.03(1H,1/2ABq,J=12.1Hz), 6.28-6.40(1H,m), 6.82-6.98(1H,m), 7.25-7.40(5H,m), 7.50-
20 7.60(1H,m).

MS (FAB) m/z: 406(M+H)⁺.

[Referential Example 437]

tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-

2-oxoacetyl}amino)-5-[(methylamino)carbonyl]cyclohexyl-
carbamate:

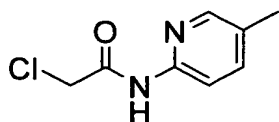


The title compound was obtained by deprotecting the
5 compound obtained in Referential Example 436 in a similar
manner to the process described in Referential Example 144
and condensing the resultant amine with the compound
obtained in Referential Example 433 in a similar manner to
the process described in Referential Example 91.

10 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.35-1.75 (3H,m), 1.39 (9H,s), 1.75-
1.86 (2H,m), 1.87-1.95 (1H,m), 2.30-2.40 (1H,m),
2.55 (3H,d,J=4.6Hz), 3.79-3.90 (2H,m), 6.73-6.90 (1H,m),
7.58-7.70 (1H,m), 8.00-8.13 (2H,m), 8.46 (1H,dd,J=2.2,1.0Hz),
8.67 (1H,d,J=7.6Hz), 10.26 (1H,s).

15 MS (ESI: negative) m/z: 452[(M-H) $^-$, Cl 35], 454[(M-H) $^-$, Cl 37].
[Referential Example 438]

2-Chloro-N-(5-methylpyridin-2-yl)acetamide hydrochloride:

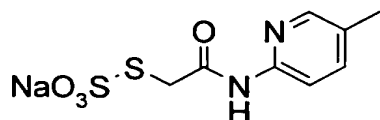


The title compound was obtained from 2-amino-5-
20 picoline in a similar manner to the process described in
Referential Example 425.

¹H-NMR (DMSO-d₆) δ: 2.30 (3H, s), 4.40 (2H, s),
7.83 (1H, d, J=8.8 Hz), 7.91 (1H, d, J=8.5 Hz), 8.21 (1H, s),
11.40 (1H, s).

[Referential Example 439]

- 5 Sodium S-{2-[(5-methylpyridin-2-yl)amino]-2-oxoethyl}thiosulfate:

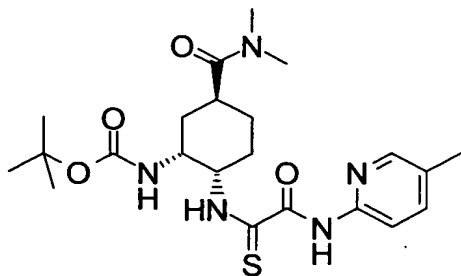


The title compound was obtained from the compound
obtained in Referential Example 438 in a similar manner to
10 the process described in Referential Example 353.

¹H-NMR (DMSO-d₆) δ: 2.24 (3H, s), 3.74 (2H, s),
7.59 (1H, d, J=8.5 Hz), 7.94 (1H, d, J=8.3 Hz), 8.12 (1H, s),
10.26 (1H, s).

[Referential Example 440]

- 15 tert-Butyl (1R,2S,5S)-5-[(dimethylamino)carbonyl]-2-({2-
[(5-methylpyridin-2-yl)amino]-2-oxoethanethioyl}amino)-
cyclohexylcarbamate:



The title compound was obtained from the compound
20 obtained in Referential Example 144 and the compound
obtained in Referential Example 439 in a similar manner to

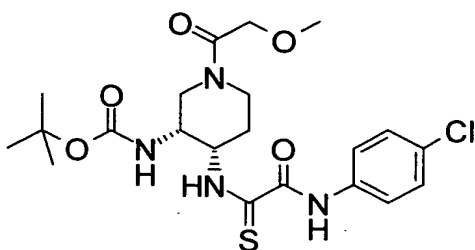
the process described in Referential Example 427.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.46(9H,s), 1.60-2.10(5H,m), 2.15-2.35(1H,m), 2.31(3H,s), 2.60-2.80(1H,m), 2.95(3H,s), 3.07(3H,s), 4.30-4.45(2H,m), 4.65-4.85(1H,m), 7.54(1H,dd, $J=8.5, 2.0\text{Hz}$), 8.06(1H,br.d), 8.18(1H,s), 9.70-9.90(1H,m), 10.48(1H,s).

MS (ESI) m/z : 464 ($\text{M}+\text{H}$) $^+$.

[Referential Example 441]

tert-Butyl (3R,4S)-4-([2-(4-chloroanilino)-2-oxoethanethioyl]amino)-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:



The title compound was obtained by deprotecting the compound obtained in Referential Example 220 by catalytic reduction in a similar manner to the process described in Referential Example 214 and condensing the resultant amine with the compound obtained in Referential Example 351 in a similar manner to the process described in Referential Example 427.

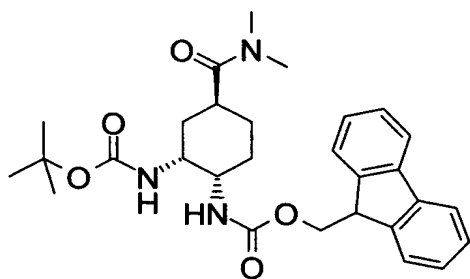
$^1\text{H-NMR}$ (CDCl_3) δ : 1.46(9H,s), 1.59-1.84(1H,m), 2.10-2.33(1H,m), 2.68-2.81(0.7H,m), 2.94-2.04(0.3H,m), 3.15-3.40(1H,m), 3.44(3H,s), 3.91-4.32(4H,m), 4.45-4.58(1H,m), 4.60-4.77(1H,m), 5.15-5.30(0.3H,br), 5.84-5.94(0.7H,m),

7.32 (2H, d, J=8.6 Hz), 7.61 (2H, d, J=8.6 Hz), 10.12 (1H, s),
10.19-10.33 (1H, br).

MS (FAB) m/z: 485 [(M+H)⁺, Cl³⁵], 487 [(M+H)⁺, Cl³⁷].

[Referential Example 442]

- 5 9H-Fluoren-9-ylmethyl (1S,2R,4S)-2-[(tert-butoxycarbonyl)-
amino]-4-[(dimethylamino)carbonyl]cyclohexylcarbamate:



- The compound (856 mg) obtained in Referential Example
144 was dissolved in acetone (10 ml), to the solution were
10 added 9-fluorenylmethyl pentafluorophenylcarbamate
(1.34 g) and sodium hydrogencarbonate (302 mg), and the
mixture was stirred at room temperature for 2.5 hours. 9-
Fluorenylmethyl pentafluorophenylcarbamate (609 mg) and
sodium hydrogencarbonate (151 mg) were additionally added,
15 and the resultant mixture was heated under reflux for 30
minutes. The solvent was distilled off under reduced
pressure, and the residue was purified by flash column
chromatography on silica gel (SI-40B, methylene
chloride:methanol = 93:7) to obtain the title compound
20 (1.47 g).

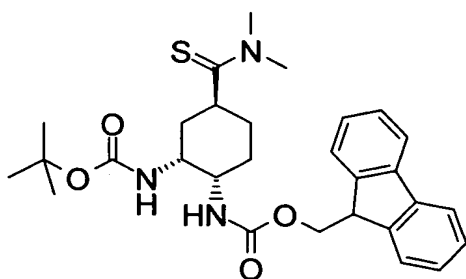
¹H-NMR (CDCl₃) δ: 1.45 (9H, s), 1.30-2.05 (6H, m),
2.63 (1H, br. s), 2.94 (3H, s), 3.04 (3H, s), 3.69 (1H, br. s),
4.15 (1H, br. s), 4.21 (1H, br. s), 4.37 (2H, br. s), 4.73 (1H, br. s),

5.41(1H,br.s), 7.29(2H,t,J=7.3Hz), 7.39(2H,t,J=7.3Hz),
7.57(2H,d,J=7.3Hz), 7.75(2H,d,J=7.3Hz).

MS (ESI) m/z: 508(M+H)⁺.

[Referential Example 443]

- 5 9H-Fluoren-9-ylmethyl (1S,2R,4S)-2-[(tert-butoxycarbonyl)-
amino]-4-[(dimethylamino)carbothioyl]cyclohexylcarbamate:



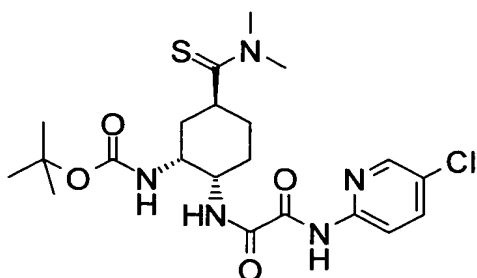
- The compound (1.26 g) obtained in Referential Example
442 was dissolved in toluene (50 ml), to the solution was
10 added a Lawesson's Reagent (1.00 g), and the mixture was
stirred at 60°C for 1 hour. Insoluble matter was removed
by filtration, and the solvent was distilled off under
reduced pressure. The residue was dissolved in ethanol (50
ml), and di-tert-butyl dicarbonate (541 mg) and sodium
15 hydrogencarbonate (208 mg) were added to the solution. The
resultant mixture was stirred at room temperature for 1
hour, the solvent was distilled off under reduced pressure,
and the residue was purified by flash column
chromatography on silica gel (hexane:ethyl acetate = 1:1 →
20 methylene chloride:methanol = 9:1) to obtain the title
compound (609 mg) as a white solid.

¹H-NMR (CDCl₃) δ: 1.43(9H,s), 1.43-2.10(6H,m),
2.92(1H,br.s), 3.31(3H,s), 3.47(3H,s), 3.74(1H,br.s),

4.09-4.19(2H,m), 4.38(2H,br.s), 4.75(1H,br), 5.29(1H,br.s),
7.29(2H,t,J=7.3Hz), 7.38(2H,t,J=7.3Hz), 7.55(2H,br.s),
7.75(2H,d,J=7.3Hz).

[Referential Example 444]

- 5 tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-
2-oxoacetyl}amino)-5-[(dimethylamino)carbothioyl]-
cyclohexylcarbamate:



- The compound (1.11 g) obtained in Referential Example
10 443 was dissolved in N,N-dimethylformamide (30 ml), to the
solution was added piperazine (3.0 ml), and the mixture
was stirred at room temperature for 15 minutes. The
solvent was distilled off under reduced pressure, and
ethyl acetate and water were added to the residue to
15 conduct liquid separation. The resultant water layer was
extracted twice with ethyl acetate. Organic layers were
combined and dried over anhydrous sodium sulfate, and the
solvent was distilled off under reduced pressure. The
residue was was condensed with the compound obtained in
20 Referential Example 433 in a similar manner to the process
described in Referential Example 91 to obtain the title
compound (629 mg).

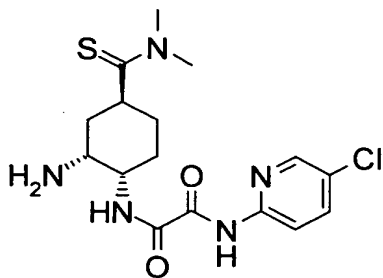
¹H-NMR (CDCl₃) δ: 1.45(9H,s), 1.48-2.23(6H,m),

2.98 (1H, br. s), 3.36 (3H, s), 3.49 (3H, s), 3.98-4.04 (1H, m),
4.22-4.25 (1H, m), 4.75 (1H, br. s), 7.70 (1H, dd, J=8.8, 2.7 Hz),
7.85 (1H, br. s), 8.16 (1H, d, J=8.8 Hz), 8.30 (1H, d, J=2.7 Hz),
9.73 (1H, s).

5 MS (FAB) m/z: 484 [(M+H)⁺, Cl³⁵], 486 [(M+H)⁺, Cl³⁷].

[Referential Example 445]

N¹-{(1S,2R,4S)-2-Amino-4-[(dimethylamino)carbothioyl]-
cyclohexyl}-N²-(5-chloropyridin-2-yl)ethanediamide
dihydrochloride:



10

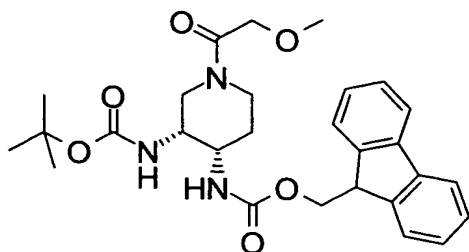
The title compound was obtained from the compound
obtained in Referential Example 444 in a similar manner to
the process described in Referential Example 69.

¹H-NMR (DMSO-d₆) δ: 1.66-2.11 (6H, m), 3.38 (3H, s),
15 3.42 (3H, s), 3.52 (1H, br. s), 3.75 (1H, br. s), 3.88 (1H, br. s),
8.03-8.09 (2H, m), 8.21 (3H, br. s), 8.48 (1H, d, J=2.2 Hz),
9.06 (1H, d, J=6.8 Hz), 10.34 (1H, s).

MS (FAB) m/z: 384 [(M+H)⁺, Cl³⁵], 386 [(M+H)⁺, Cl³⁷].

[Referential Example 446]

20 9H-Fluoren-9-ylmethyl (3R,4S)-3-[(tert-butoxycarbonyl)-
amino]-1-(2-methoxyacetyl)piperidin-4-ylcarbamate:



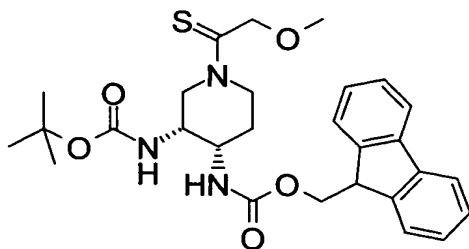
The title compound was obtained by deprotecting the compound obtained in Referential Example 220 by catalytic reduction in a similar manner to the process described in Referential Example 214 and treating the resultant amine in a similar manner to the process described in Referential Example 442.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 1.55-1.80 (1H, m), 1.92-2.20 (1H, m), 2.70-3.35 (2H, m), 3.44 (3H, s), 3.77-4.90 (10H, m), 5.29-5.45 (0.6H, br), 5.75-5.90 (0.4H, br), 7.26-7.34 (2H, m), 7.39 (2H, t, $J=7.6\text{Hz}$), 7.55-7.65 (2H, m), 7.76 (2H, d, $J=7.6\text{Hz}$).

MS (FAB) m/z : 510 ($\text{M}+\text{H}$) $^+$.

[Referential Example 447]

9H-Fluoren-9-ylmethyl (3R,4S)-3-[(tert-butoxycarbonyl)amino]-1-(2-methoxyethanethioyl)piperidin-4-ylcarbamate:



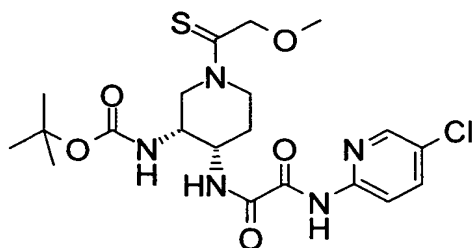
The title compound was obtained from the compound obtained in Referential Example 446 in a similar manner to the process described in Referential Example 443.

¹H-NMR (CDCl₃) δ: 1.48 (9H, s), 1.50-1.80 (1H, m), 2.07-
2.23 (1H, m), 3.04-3.18 (0.5H, m), 3.25-3.37 (0.5H, m),
3.44 (1.5H, s), 3.47 (1.5H, s), 3.88-4.75 (9H, m), 5.00-
5.70 (2H, br), 5.98-6.23 (1H, br), 7.26-7.29 (2H, m),
5 7.39 (2H, t, J=7.3 Hz), 7.55-7.68 (2H, m), 7.77 (2H, d, J=7.3 Hz).

MS (FAB) m/z: 526 (M+H)⁺.

[Referential Example 448]

tert-Butyl (3R,4S)-4-({2-[(5-chloropyridin-2-yl)amino]-2-
oxoacetyl}amino)-1-(2-methoxyethanethioyl)piperidin-3-
10 ylcarbamate:



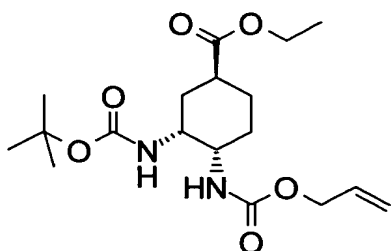
The title compound was obtained by treating the
compound obtained in Referential Example 447 with
diethylamine in a similar manner to the process described
15 in Referential Example 444 to conduct deprotection and
then condensing the resultant compound with the compound
obtained in Referential Example 433.

¹H-NMR (CDCl₃) δ: 1.47 (9H, s), 1.73-1.88 (1H, m), 2.07-
2.22 (1H, m), 3.05-3.15 (1H, m), 3.27-3.42 (1H, m), 3.45 (1H, s),
20 3.48 (2H, s), 4.10-4.54 (5H, m), 5.12-5.21 (0.3H, br), 5.48-
5.56 (0.7H, br), 5.61-5.74 (1H, br), 7.70 (1H, dd, J=8.5, 2.0 Hz),
8.21 (1H, d, J=8.5 Hz), 8.31 (1H, d, J=2.0 Hz), 8.42-8.60 (1H, br),
9.72 (1H, br. s).

MS (ESI) m/z: 486[(M+H)⁺,Cl³⁵], 488[(M+H)⁺,Cl³⁷].

[Referential Example 449]

Ethyl (1S,3R,4S)-4-([(allyloxy)carbonyl]amino)-3-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate:



5

A 10% palladium on carbon catalyst (10.2 g) was added to a solution of the compound (10.0 g) obtained in Referential Example 141 in a mixed solvent of tetrahydrofuran (40 ml) and ethanol (40 ml), and the mixture was stirred at room temperature for 63 hours under a hydrogen atmosphere. After the catalyst was removed by filtration, the resultant filtrate was concentrated under reduced pressure. After the resultant colorless oil was dissolved in tetrahydrofuran (25 ml), and pyridine (2.3 ml) was added to the solution at room temperature, allylchloroformate (2.70 ml) was added dropwise at 0°C, and the mixture was stirred for 20 minutes. After ice and ethyl acetate were added to the reaction mixture, and the resultant mixture was stirred for 5 minutes, A 10% aqueous solution of citric acid was added to acidify the mixture. The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over

10

15

20

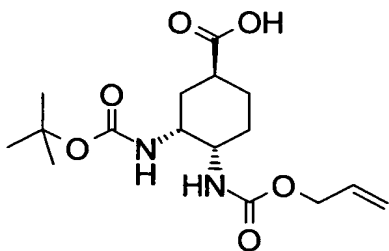
anhydrous sodium sulfate and then concentrated under reduced pressure. The resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 40:1) to obtain the title compound
5 (6.03 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.25(3H,t,J=7.1Hz), 1.31-1.40(1H,m), 1.45(9H,s), 1.51-1.65(1H,m), 1.72-1.86(1H,m), 1.89-2.10(3H,m), 2.25-2.50(1H,br), 3.63-3.72(1H,m), 4.03-4.15(1H,br), 4.13(2H,q,J=7.1Hz), 4.49-4.59(2H,m), 4.60-10 4.75(1H,m), 5.20(1H,d,J=10.5Hz), 5.22-5.32(1H,br), 5.29(1H,dd,J=17.1,1.7Hz), 5.85-5.97(1H,m).

MS (ESI) m/z : 371($\text{M}+\text{H}$) $^+$.

[Referential Example 450]

(1S,3R,4S)-4-{[(Allyloxy)carbonyl]amino}-3-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylic acid:
15



The title compound was obtained from the compound obtained in Referential Example 449 in a similar manner to the process described in Referential Example 142.

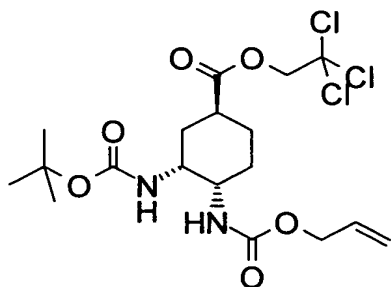
20 $^1\text{H-NMR}$ (CDCl_3) δ : 1.35-2.15(6H,br), 1.45(9H,s), 2.35-2.65(1H,br), 3.65-3.75(1H,m), 4.00-4.15(1H,br), 4.48-4.63(2H,m), 4.63-4.80(1H,br), 5.03-5.33(1H,br), 5.21(1H,d,J=10.3Hz), 5.29(1H,dd,J=17.1,1.5Hz), 5.86-

5.97 (1H, m).

MS (ESI) m/z : 343 (M+H)⁺.

[Referential Example 451]

2,2,2-Trichloroethyl (1S,3R,4S)-4-[[allyloxy]carbonyl]-
5 amino}-3-[(tert-butoxycarbonyl)amino]cyclohexane-
carboxylate:



1-[(3S,5S)-3-allyloxycarbonyl-5-[(tert-butoxycarbonyl)amino]cyclohexyl]carbamate
hydrochloride (4.99 g), 1-hydroxybenzotriazole (2.81 g),
10 2,2,2-trichloroethanol (4.15 ml) and 4-
dimethylaminopyridine (4.15 g) were added to a solution of
the compound (5.93 g) obtained in Referential Example 450
in N,N-dimethylformamide (40 ml), and the mixture was
stirred at room temperature for 1.5 hours. After the
15 reaction mixture was concentrated under reduced pressure,
ethyl acetate and water were added to the residue. The
resultant water layer was extracted with ethyl acetate,
and organic layers were combined, washed with a 10%
aqueous solution of citric acid, a saturated aqueous
20 solution of sodium hydrogencarbonate and a saturated
aqueous solution of sodium chloride, dried over anhydrous
sodium sulfate and then concentrated under reduced
pressure. The residue was purified by column

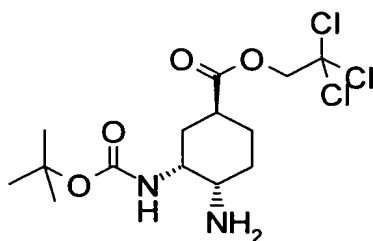
chromatography on silica gel (methylene chloride:methanol = 40:1) to obtain the title compound (8.88 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.35-1.50 (1H,m), 1.46 (9H,s), 1.55-1.73 (1H,m), 1.77-2.22 (4H,m), 2.50-2.65 (1H,br), 3.66-3.75 (1H,m), 4.05-4.20 (1H,m), 4.50-4.60 (2H,m), 4.60-4.80 (1H,br), 4.71 (1H,d,J=11.8Hz), 4.77 (1H,d,J=11.8Hz), 5.18-5.34 (1H,br), 5.20 (1H,d,J=10.5Hz), 5.30 (1H,dd,J=17.4,1.0Hz), 5.86-5.97 (1H,m).

MS (ESI) m/z : 473 [$(\text{M}+\text{H})^+$, $3\times\text{Cl}^{35}$], 475 [$(\text{M}+\text{H})^+$, $2\times\text{Cl}^{35}$, Cl^{37}], 477 [$(\text{M}+\text{H})^+$, Cl^{35} , $2\times\text{Cl}^{37}$].

[Referential Example 452]

2,2,2-Trichloroethyl (1S,3R,4S)-4-amino-3-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate:



Diethylamine (20 ml) and tetrakis(triphenylphosphine)palladium (719 mg) were added to a solution of the compound (8.83 g) obtained in Referential Example 451 in tetrahydrofuran (35 ml), and the mixture was stirred at room temperature for 2.5 hours under argon. A 10% aqueous solution (250 ml) of citric acid was added to the reaction mixture to acidify it, and diethyl ether was added thereto. After the resultant water layer was washed with diethyl ether, sodium carbonate was added to the water layer to

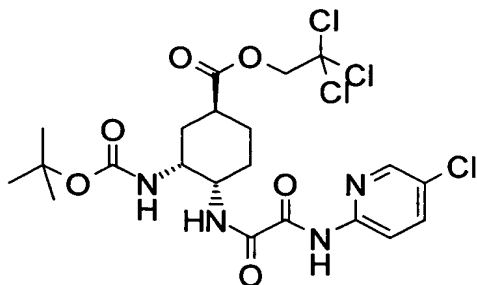
alkalify it, and the water layer was extracted with methylene chloride. The resultant methylene chloride layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated under reduced pressure to obtain the title compound (4.35 g).

¹H-NMR (CDCl₃) δ: 1.20-1.50 (3H,m), 1.46 (9H,s), 1.58-1.69 (1H,m), 1.70-1.81 (2H,m), 1.98-2.07 (1H,m), 2.22-2.31 (1H,m), 2.55-2.66 (1H,m), 2.97-3.04 (1H,m), 3.79-3.93 (1H,br), 4.70 (1H,d,J=12.0Hz), 4.75-4.85 (1H,br), 4.78 (1H,d,J=12.0Hz).

MS (ESI) m/z: 389 [(M+H)⁺, 3xCl³⁵], 391 [(M+H)⁺, 2xCl³⁵, Cl³⁷], 393 [(M+H)⁺, Cl³⁵, 2xCl³⁷].

[Referential Example 453]

2,2,2-Trichloroethyl (1S,3R,4S)-3-[(tert-butoxycarbonyl)-amino]-4-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}-amino)cyclohexanecarboxylate:



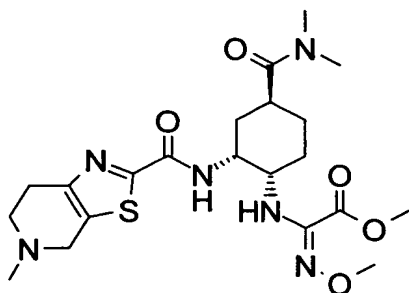
The title compound was obtained by condensing the compound obtained in Referential Example 452 with the compound obtained in Referential Example 433 in a similar manner to the process described in Referential Example 91.

¹H-NMR (CDCl₃) δ: 1.46 (9H,s), 1.50-1.63 (1H,m), 1.65-

1.79 (2H, m), 1.87-2.08 (2H, m), 2.10-2.22 (2H, m), 2.50-
 2.70 (1H, br), 3.94-4.02 (1H, m), 4.17-4.30 (1H, br),
 4.73 (1H, d, J=12.0 Hz), 4.78 (1H, d, J=12.0 Hz),
 7.70 (1H, dd, J=8.8, 2.4 Hz), 7.90-8.07 (1H, br),
 5 8.18 (1H, d, J=8.8 Hz), 8.31 (1H, d, J=2.4 Hz), 9.72 (1H, br. s).
 MS (ESI) m/z: 571 [(M+H)⁺, 3xCl³⁵], 573 [(M+H)⁺, 2xCl³⁵, Cl³⁷],
 575 [(M+H)⁺, Cl³⁵, 2xCl³⁷].

[Referential Example 454]

Methyl 2-[(1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-
 10 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 yl)carbonyl]amino]cyclohexyl)amino]-2-(methoxyimino)-
 acetate:



The compound (435 mg) obtained in Referential Example
 15 144 and methyl 2-(methoxyimino)-2-(methylsulfonyl)acetate
 (W099/67209) (233 mg) were dissolved in tetrahydrofuran (5
 ml), triethylamine (332 µl) was added to this solution,
 and the mixture was stirred overnight at 70°C. The
 reaction mixture was concentrated under reduced pressure,
 20 and methylene chloride and a saturated aqueous solution of
 sodium hydrogencarbonate were added to the residue to
 conduct liquid separation. The resultant oil layer was

dried over anhydrous sodium sulfate. After concentrating the oil layer, the resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 91:9) to obtain the title compound

5 (111 mg).

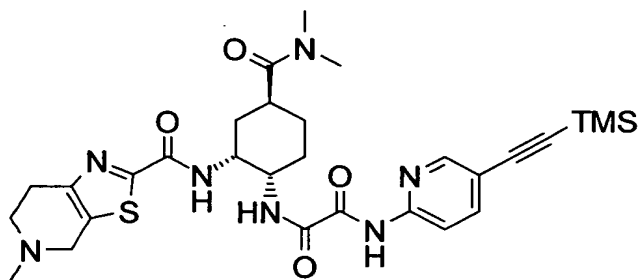
$^1\text{H-NMR}$ (CDCl_3) δ : 1.42-2.10 (6H,m), 2.52 (3H,s), 2.70-3.10 (11H,m), 3.71 (2H,br.s), 3.83 (3H,s), 3.84 (3H,s), 4.22-4.35 (1H,m), 4.55-4.65 (1H,m), 5.16 (1H,d, $J=8.8\text{Hz}$), 7.25-7.30 (1H,m).

10 MS (ESI) m/z : 481 ($\text{M}+\text{H}$) $^+$.

[Referential Example 455]

N^1 -((1S,2R,4S)-4-[(Dimethylamino)carbothioyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazol[5,4-c]pyridin-2-yl)carbonyl]amino)cyclohexyl)- N^2 -{5-[2-

15 (trimethylsilyl)ethynyl]pyridin-2-yl}ethanediamide:



The compound (658 mg) obtained in Referential Example 204 was dissolved in tetrahydrofuran (10 ml), N,N -dimethylformamide (10 ml) and triethylamine (20 ml), and
20 triphenylphosphine (87 mg), trimethylsilylacetylene (471 μl), palladium acetate (50 mg) were added to the solution. The resultant mixture was stirred at 80°C for 14 hours

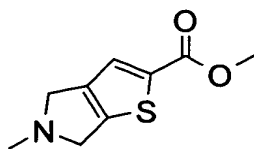
under an argon atmosphere. The reaction mixture was filtered through Celite, and the filtrate was fully washed with methylene chloride. Water was added to the filtrate to conduct liquid separation, and the resultant organic layer was decolorized with activated carbon (about 3 g) and dried over anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 93:7) to obtain the title compound (360 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 0.25 (9H, s), 1.66-2.13 (6H, m), 2.52 (3H, s), 2.78-2.96 (8H, m), 3.05 (3H, s), 3.70 (1H, d, $J=15.4\text{Hz}$), 3.73 (1H, d, $J=15.4\text{Hz}$), 4.08-4.15 (1H, m), 4.66-4.69 (1H, m), 7.42 (1H, d, $J=8.4\text{Hz}$), 7.77 (1H, dd, $J=8.4, 2.1\text{Hz}$), 8.03 (1H, d, $J=8.1\text{Hz}$), 8.13 (1H, d, $J=8.8\text{Hz}$), 8.43 (1H, d, $J=2.1\text{Hz}$), 9.74 (1H, s).

MS (ESI) m/z : 610 ($\text{M}+\text{H}$) $^+$.

[Referential Example 456]

Methyl 5-methyl-5,6-dihydro-4H-thieno[2,3-c]pyrrole-2-carboxylate:



Methyl 4,5-bis(chloromethyl)-2-thiophenecarboxylic acid (D. J. Zwanenburg and Hans Wynberg, J. Org. Chem., 34, 333-340, (1969)) (520 mg) was dissolved in acetonitrile (600 ml), methylamine (40% methanol solution, 722 μl) was

added to the solution, and the mixture was stirred at room temperature for 3 days. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene

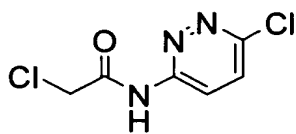
5 chloride:methanol = 1:0 → 19:1) to obtain the title compound (176 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.63(3H,s), 3.82-3.83(2H,m), 3.86(3H,s), 3.97-3.99(2H,m), 7.51(1H,s).

MS (ESI) m/z : 198 ($\text{M}+\text{H}$) $^+$.

10 [Referential Example 457]

2-Chloro-N-(6-chloropyridazin-3-yl)acetamide:

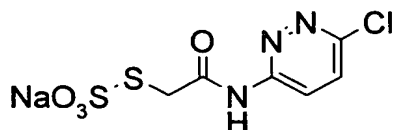


3-Amino-6-chloropyridazine (10.4 g) was dissolved in N,N-dimethylformamide (200 ml), chloroacetyl chloride
15 (7.48 ml) was added to the solution, and the mixture was stirred at room temperature for 1 hour. The solvent was distilled off under reduced pressure, and ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue. Solids
20 deposited were collected by filtration and washed with ethyl acetate and water to obtain the title compound (9.39 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 4.30(2H,s), 7.56(1H,d,J=9.3Hz), 8.51(1H,d,J=9.3Hz), 9.68(1H,br.s).

25 [Referential Example 458]

Sodium S-{2-[(6-chloropyridazin-3-yl)amino]-2-oxoethyl}thiosulfate:

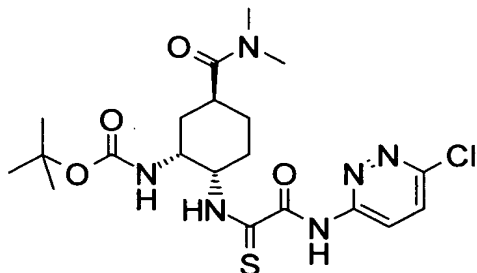


The title compound was obtained from the compound
5 obtained in Referential Example 457 in a similar manner to the process described in Referential Example 353.

¹H-NMR (DMSO-d₆) δ: 3.84(2H,s), 7.87(1H,d,J=9.4Hz), 8.36(1H,d,J=9.4Hz), 11.21(1H,br.s).

[Referential Example 459]

10 tert-Butyl (1R,2S,5S)-2-({2-[(6-chloropyridazin-3-yl)amino]-2-oxoethanethioyl}amino)-5-[(dimethylamino)-carbothioyl]cyclohexylcarbamate:



The title compound was obtained from the compound
15 obtained in Referential Example 458 and the compound obtained in Referential Example 144 in a similar manner to the process described in Referential Example 427.

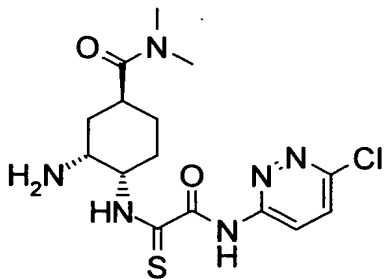
¹H-NMR (CDCl₃) δ: 1.35-1.58(10H,m), 1.71-1.80(1H,m), 1.86-1.94(2H,m), 2.09(1H,br.s), 2.30(1H,br.s), 2.96(3H,s),
20 3.08(3H,s), 4.36(2H,br.s), 4.79(1H,br.s), 5.30(1H,br.s), 7.54(1H,d,J=9.0Hz), 8.47(1H,d,J=9.0Hz), 10.03(1H,br.s),

11.03(1H,s) .

[Referential Example 460]

(1S,3R,4S)-3-Amino-4-((2-[(6-chloropyridazin-3-yl)amino]-2-oxoethanethioyl)amino)-N,N-dimethylcyclohexane-

5 carboxamide hydrochloride:



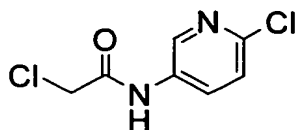
The title compound was obtained from the compound obtained in Referential Example 459 in a similar manner to the process described in Referential Example 69.

10 ¹H-NMR (DMSO-d₆) δ: 1.45-1.53(1H,m), 1.73-1.85(3H,m), 2.03-2.07(1H,m), 2.15-2.24(1H,m), 2.82(3H,s), 3.08(3H,s), 3.32-3.37(1H,m), 4.06(1H,br.s), 4.39(1H,br.s), 8.01(1H,d,J=9.3Hz), 8.37(1H,d,J=9.3Hz), 8.43(3H,br.s), 11.11(1H,d,J=6.6Hz), 11.37(1H,s).

15 MS (FAB) m/z: 385[(M+H)⁺,Cl³⁵], 387[(M+H)⁺,Cl³⁷].

[Referential Example 461]

2-Chloro-N-(6-chloropyridin-3-yl)acetamide:

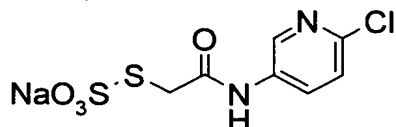


20 The title compound was obtained from 5-amino-2-chloropyridine in a similar manner to the process described in Referential Example 457.

¹H-NMR (CDCl₃) δ: 4.22 (2H, s), 7.34 (1H, d, J=8.5 Hz),
8.14 (1H, dd, J=8.5, 2.7 Hz), 8.30 (1H, br. s), 8.45 (1H, d, J=2.7 Hz).

[Referential Example 462]

Sodium S-{2-[(6-chloropyridin-3-yl)amino]-2-oxoethyl}-
5 thiosulfate:

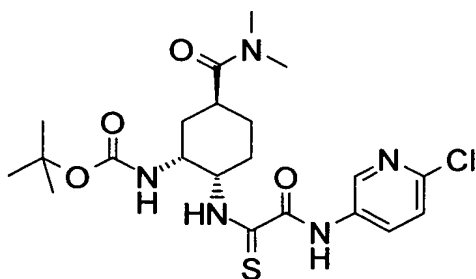


The title compound was obtained from the compound
obtained in Referential Example 461 in a similar manner to
the process described in Referential Example 353.

10 ¹H-NMR (DMSO-d₆) δ: 3.77 (2H, s), 7.47 (1H, d, J=8.8 Hz),
8.04 (1H, dd, J=8.8, 2.7 Hz), 8.57 (1H, d, J=2.7 Hz), 10.51 (1H, s).

[Referential Example 463]

tert-Butyl (1R,2S,5S)-2-({2-[(6-chloropyridin-3-yl)amino]-
2-oxoethanethioyl}amino)-5-[(dimethylamino)carbonyl]-
15 cyclohexylcarbamate:



The title compound was obtained from the compound
obtained in Referential Example 462 and the compound
obtained in Referential Example 144 in a similar manner to
20 the process described in Referential Example 427.

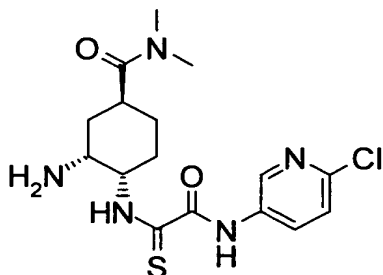
¹H-NMR (CDCl₃) δ: 1.46 (9H, br. s), 1.60-2.23 (6H, m),

2.68 (1H, br.s), 2.96 (3H, s), 3.08 (3H, s), 4.34-4.38 (2H, m),
4.78 (1H, m), 7.33 (1H, d, J=8.5 Hz), 8.09 (1H, br.s), 8.63 (1H, s),
9.91 (1H, br.s), 10.24 (1H, s).

MS (ESI) m/z: 506 [(M+Na)⁺, Cl³⁵], 508 [(M+Na)⁺, Cl³⁷].

5 [Referential Example 464]

(1S, 3R, 4S)-3-Amino-4-({2-[(6-chloropyridin-3-yl)amino]-2-oxoethanethioyl}amino)-N,N-dimethylcyclohexane-carboxamide hydrochloride:



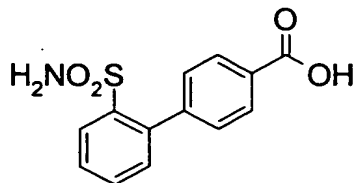
10 The title compound was obtained from the compound
obtained in Referential Example 463 in a similar manner to
the process described in Referential Example 69.

¹H-NMR (DMSO-d₆) δ: 1.46-1.49 (1H, m), 1.79-1.81 (3H, m), 1.99-
2.03 (1H, m), 2.14-2.16 (1H, m), 2.82 (3H, s), 3.06 (3H, s), 3.25-
15 3.28 (1H, m), 3.99 (1H, br.s), 4.30-4.60 (1H, br),
7.55 (1H, d, J=8.7 Hz), 8.26 (1H, dd, J=8.7, 2.4 Hz), 8.38 (3H, br.s),
8.85 (1H, d, J=2.4 Hz), 10.90 (1H, d, J=6.8 Hz), 11.07 (1H, s).

MS (FAB) m/z: 384 [(M+H)⁺, Cl³⁵], 386 [(M+H)⁺, Cl³⁷].

[Referential Example 465]

20 2'-Aminosulfonyl-1,1'-biphenyl-4-carboxylic acid:

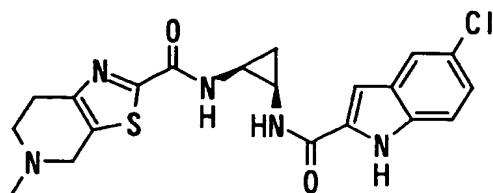


2-Bromobenzenesulfonamide (800 mg) and 4-carboxyphenylboronic acid (563 mg) were suspended in a mixed solvent of toluene (5 ml) and water (5 ml).

5 Tetrakis(triphenylphosphine)palladium (392 mg) and anhydrous sodium carbonate (1.08 g) were successively added to the suspension, and the mixture was heated under reflux overnight. After the reaction mixture was cooled to room temperature, diethyl ether and water were added to
 10 conduct liquid separation. The resultant organic layer was extracted twice with water. The resultant water layers were all combined, and 12N hydrochloric acid was added to this solution to acidify it. The solution was concentrated to about 20 ml under reduced pressure. Colorless powder
 15 deposited was collected by filtration and dried under reduced pressure to obtain the title compound (539 mg).
 MS (EI) m/z: 277M⁺.

[Example 1]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}cyclopropyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
 20 hydrochloride:



1-Hydroxybenzotriazole monohydrate (71 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg) were added to a solution with the compound (108 mg) obtained in Referential Example 59 and the compound (124 mg) obtained in Referential Example 10 dissolved in N,N-dimethylformamide (3 ml) at room temperature, and the mixture was stirred for 8 days. After concentrating the reaction mixture under reduced pressure using a vacuum pump, water (50 ml) and a saturated aqueous solution (50 ml) of sodium hydrogencarbonate were added to the residue to conduct extraction with methylene chloride. The resultant organic layers were combined and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:methanol = 10:1). After 1N hydrochloric acid, methylene chloride and methanol were added to the thus-obtained amorphous substance, the mixture was concentrated to obtain the title compound (72 mg).

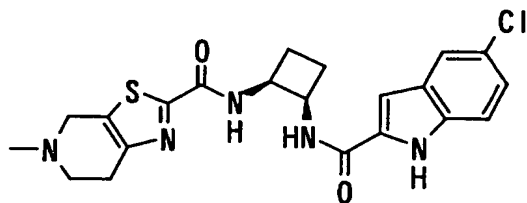
$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.15-1.35 (2H,m), 2.88 (3H,s), 2.95-3.25 (4H,m), 3.35-3.75 (2H,m), 4.32-4.45 (1H,m),

4.68 (1H, br, J=15.4Hz), 7.08 (1H, s), 7.17 (1H, dd, J=8.6, 2.1Hz),
7.41 (1H, d, J=8.6Hz), 7.70 (1H, s), 8.50 (1H, br, J=11.0Hz),
8.56 (1H, br. s), 11.56 (1H, br, J=19.3Hz), 11.86 (1H, s).

MS (FAB) m/z: 430 (M+H)⁺.

5 [Example 2]

N-((1R*,2S*)-2-[[(5-Chloroindol-2-yl) carbonyl] amino]-
cyclobutyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridine-2-carboxamide hydrochloride:



10 The compound (136 mg) obtained in Referential
Example 10, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride (255 mg) and 1-hydroxybenzotriazole
monohydrate (90 mg) were added to a solution with the
compound (117 mg) obtained in Referential Example 60
15 dissolved in N,N-dimethylformamide (5 ml), and the mixture
was stirred overnight at room temperature. The solvent was
then distilled off under reduced pressure using a vacuum
pump, and methylene chloride and a saturated aqueous
solution of sodium hydrogencarbonate were added to the
20 residue to conduct liquid separation. The resultant
organic layer was washed with saturated aqueous solution
of sodium chloride and dried over anhydrous sodium sulfate,
the solvent was distilled off under reduced pressure, and

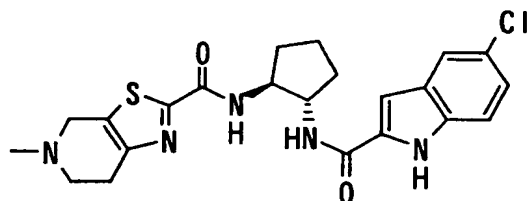
the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 7:93). After ethyl acetate and a 1N ethanol solution of hydrochloric acid were added to the thus-obtained compound to acidify it, and the solvent was distilled off under reduced pressure. Ethyl acetate was added again, and precipitate formed was collected by filtration and dried to obtain the title compound (56 mg).

¹H-NMR (DMSO-d₆) δ: 2.00-2.35(4H,m), 2.88(3H,m), 3.10(2H,br.s), 3.20-3.75(3H,m), 4.20-4.85(3H,m), 7.09(1H,s), 7.16(1H,d,J=8.8Hz), 7.38(1H,d,J=8.8Hz), 7.71(1H,s), 8.63(1H,d,J=8.3Hz), 8.85(1H,d,J=8.6Hz), 10.85-11.20(1H,br), 11.81(1H,s).

MS (FAB) m/z: 444(M+H)⁺.

[Example 3]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclopentyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



5-Chloroindole-2-carboxylic acid (80 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (98 mg), 1-hydroxybenzotriazole monohydrate (23 mg) and triethylamine (141 μl) were added to a solution with the

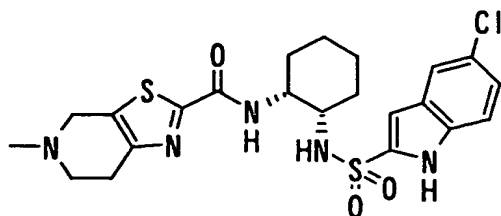
compound (120 mg) obtained in Referential Example 62 dissolved in N,N-dimethylformamide (5 ml), and the mixture was stirred at room temperature for 3 days. The solvent was distilled off under reduced pressure, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 93:7). After methylene chloride (5 ml) and a 1N ethanol solution (282 μ l) of hydrochloric acid were added to the thus-obtained pale yellow solid, ethyl acetate was added, and precipitate formed was collected by filtration to obtain the title compound (109 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.64-1.74 (4H,m), 1.98-2.02 (2H,m), 2.89 (3H,s), 3.14 (2H,br.s), 3.47-3.65 (2H,m), 4.29-4.63 (4H,m), 7.10 (1H,d,J=1.5Hz), 7.14 (1H,dd,J=8.5,2.0Hz), 7.38 (1H,d,J=8.5Hz), 7.68 (1H,d,J=2.0Hz), 8.55 (1H,d,J=8.5Hz), 8.91 (1H,d,J=8.5Hz), 11.49 (1H,br.s), 11.76 (1H,s).

MS (ESI) m/z : 458 ($\text{M}+\text{H}$) $^+$.

[Example 4]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)sulfonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



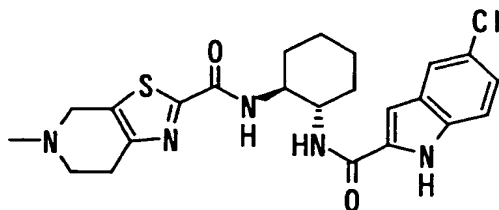
The compound (400 mg) obtained in Referential Example 67 was suspended in methylene chloride (10 ml), triethylamine (0.514 ml) and (5-chloro-1-phenylsulfonylindole-2-sulfonyl chloride (Japanese Patent Application Laid-Open No. 2000-119253) (319 mg) were added, and the mixture was stirred at room temperature for 15 minutes. After water was added to the reaction mixture to conduct liquid separation, the resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 100:3) to obtain a pale yellow foamy substance. This substance was dissolved in tetrahydrofuran (3 ml), and methanol (2 ml) and a 1N aqueous solution (1.5 ml) of sodium hydroxide were added to heat the mixture under reflux for 2 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride and 1N hydrochloric acid were added to the residue to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica

gel (methylene chloride:methanol = 100:3). 1N Hydrochloric acid (1 ml) was added to the resultant product, and the mixture was concentrated under reduced pressure to obtain the title compound (108 mg).

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.20-1.78 (8H,m), 2.94 (3H,s), 3.13 (2H,br.s), 3.22-3.40 (1H,m), 3.44-3.70 (3H,m), 3.83-3.95 (1H,m), 4.20-4.70 (1H,m), 6.78 (1H,s), 7.18-7.30 (2H,m), 7.44 (1H,s), 7.69 (1H,br.s), 8.09 (1H,br.s), 11.92 (1H,s).
MS (FAB) m/z : 508 ($\text{M}+\text{H}$) $^+$.

10 [Example 5]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



15 5-Chloroindole-2-carboxylic acid (109 mg), 1-hydroxybenzotriazole monohydrate (9 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (321 mg) and triethylamine (0.232 ml) were added to a solution with the compound (300 mg) obtained in

20 Referential Example 65 dissolved in N,N-dimethylformamide (20 ml), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure using a vacuum pump, and methylene

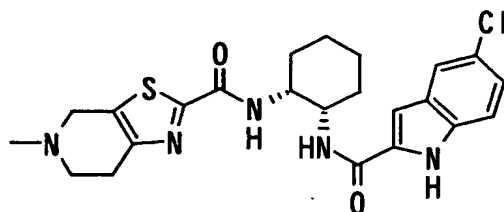
chloride and water were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 25:1) to obtain a colorless foamy substance. This substance was suspended in 1N hydrochloric acid (1 ml), and the suspension was concentrated under reduced pressure to obtain the title compound (203 mg).

¹H-NMR (DMSO-d₆) δ: 1.25-1.40 (2H,m), 1.46-1.81 (4H,m), 1.88-1.98 (2H,m), 2.89 (3H,s), 3.00-3.76 (5H,m), 3.86-3.97 (1H,m), 4.00-4.10 (1H,m), 4.25-4.72 (1H,m), 7.03 (1H,s), 7.12 (1H,dd,J=8.5,1.2Hz), 7.38 (1H,d,J=8.5Hz), 7.64 (1H,s), 8.28 (1H,d,J=8.5Hz), 8.54 (1H,d,J=8.5Hz), 11.70 (1H,s).

MS (FAB) m/z: 472 (M+H)⁺.

[Example 6]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:

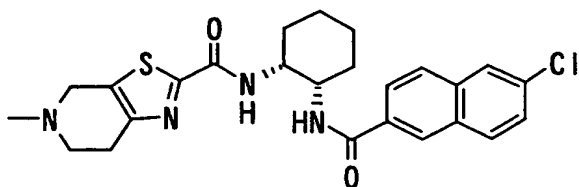


The title compound was obtained from the compound obtained in Referential Example 67 and 5-chloroindole-2-carboxylic acid in a similar manner to Example 5.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.35-1.70 (6H,m), 1.80-2.06 (2H,m),
 2.89 (3H,s), 3.00-3.27 (2H,m), 3.35-3.51 (1H,m), 3.57-
 3.82 (1H,m), 4.15-4.30 (2H,m), 4.32-4.48 (1H,m), 4.60-
 4.74 (1H,m), 7.15 (1H,s), 7.17 (1H,dd, $J=8.8, 2.0\text{Hz}$),
 5 7.41 (1H,d, $J=8.6\text{Hz}$), 7.70 (1H,d, $J=2.0\text{Hz}$), 8.14 (1H,br.s),
 8.36-8.48 (1H,m), 11.51 (1H,br.s), 11.86 (1H,s).
 MS (FAB) m/z : 472 ($\text{M}+\text{H}$) $^+$.

[Example 7]

N-{(1R*,2S*)-2-[(6-Chloronaphthoyl)amino]cyclohexyl}-5-
 10 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-
 carboxamide hydrochloride:



The title compound (186 mg) was obtained by
 dissolving the compound (275 mg) obtained in Referential
 15 Example 67, 6-chloronaphthalene-2-carboxylic acid (Eur. J.
 Chem. Chim. Ther., 1984, Vol. 19, pp. 205-214) (148 mg),
 triethylamine (0.298 ml) and 1-hydroxybenzotriazole
 monohydrate (11 mg) in N,N-dimethylformamide (20 ml) and
 causing 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
 20 hydrochloride (412 mg) to react in a similar manner to
 Example 5.

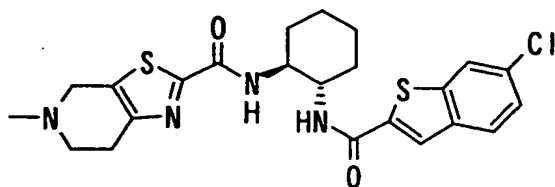
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.40-1.56 (2H,m), 1.57-1.77 (4H,m), 1.90-
 2.10 (2H,m), 2.90 (3H,s), 3.13 (2H,br.s), 3.28-3.74 (2H,m),

4.26 (2H, br. s), 4.30-4.74 (2H, m), 7.59 (1H, d, J=8.6 Hz),
7.90 (1H, d, J=8.6 Hz), 7.98 (1H, d, J=8.3 Hz), 8.03-8.11 (2H, m),
8.25-8.58 (3H, m), 11.52 (1H, br. s).

MS (FAB) m/z: 483 (M+H)⁺.

5 [Example 8]

N-((1R*,2R*)-2-[[(6-Chloro-1-benzothiophen-2-yl) carbonyl] amino] cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



10

The title compound (239 mg) was obtained by dissolving the compound (255 mg) obtained in Referential Example 65, 6-chlorobenzo[b]thiophene-2-carboxylic acid (Japanese Patent Application Laid-Open No. 2000-119253)

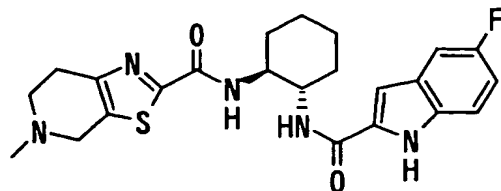
15 (141 mg), triethylamine (0.276 ml) and 1-hydroxybenzotriazole monohydrate (10 mg) in N,N-dimethylformamide (20 ml) and causing 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (382 mg) to react in a similar manner to Example 5.

20 ¹H-NMR (DMSO-d₆) δ: 1.20-1.98 (8H, m), 2.88 (3H, s), 3.00-3.72 (4H, m), 3.84-4.09 (2H, m), 4.20-4.75 (2H, m), 7.41 (1H, dd, J=8.6, 1.7 Hz), 7.91 (1H, d, J=8.6 Hz), 7.99 (1H, s), 8.12 (1H, s), 8.54-8.67 (2H, m), 11.53 (1H, br. s).

MS (FAB) m/z: 489 (M+H)⁺.

[Example 9]

N-((1R*,2R*)-2-[[(5-Fluoroindol-2-yl)carbonyl]amino]-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



5

The title compound was obtained from the compound obtained in Referential Example 65 and 5-fluoroindole-2-carboxylic acid in a similar manner to Example 5.

¹H-NMR (DMSO-d₆) δ: 1.20-1.38 (2H,m), 1.40-1.57 (1H,m), 1.54-1.68 (1H,m), 1.71 (2H,d,J=7.3Hz), 1.88 (2H,d,J=12.0Hz), 2.86 (3H,s), 2.95-3.24 (2H,m), 3.40 (1H,br.s), 3.63 (1H,br.s), 3.90 (1H,br.s), 3.97-4.10 (1H,m), 4.20-4.44 (1H,m), 4.53-4.70 (1H,m), 6.98 (1H,dd,J=9.2,2.3Hz), 7.01 (1H,s), 7.31-7.39 (2H,m), 8.26 (1H,d,J=8.6Hz), 8.59 (1H,d,J=8.4Hz), 11.21 (1/2H,br.s), 11.42 (1/2H,br.s), 11.60 (1H,s).

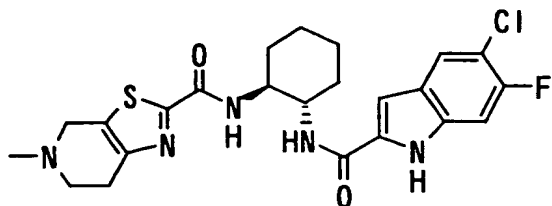
15

MS (ESI) m/z: 456 (M+H)⁺.

[Example 10]

N-((1R*,2R*)-2-[[(5-Chloro-6-fluoroindol-2-yl)carbonyl]amino]cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-
[5,4-c]pyridine-2-carboxamide hydrochloride

20

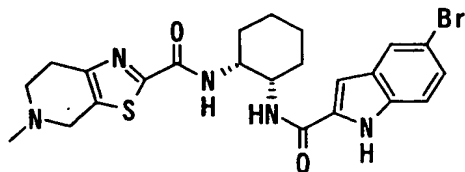


The title compound was obtained from the compound obtained in Referential Example 65 and the compound obtained in Referential Example 23 in a similar manner to Example 5.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.20-1.40 (2H,m), 1.40-1.80 (4H,m), 1.80-2.00 (2H,m), 2.87 (3H,s), 3.01 (2H,br.s), 3.30-3.80 (2H,m), 3.81-3.97 (2H,m), 4.20-4.80 (2H,m), 7.06 (1H,s), 7.28 (1H,d, $J=10.0\text{Hz}$), 7.86 (1H,d, $J=7.3\text{Hz}$), 8.32 (1H,d, $J=8.5\text{Hz}$), 8.59 (1H,d, $J=8.5\text{Hz}$), 11.77 (1H,s).
 MS (FAB) m/z : 490 ($\text{M}+\text{H}$) $^+$.

[Example 11]

N-((1R*,2S*)-2-{[(5-Bromoindol-2-yl)carbonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 67 and 5-bromoindole-2-carboxylic acid in a similar manner to Example 5.

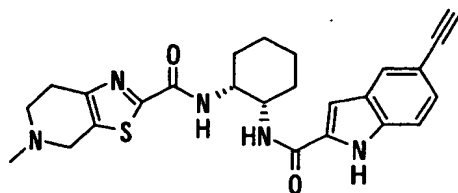
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.43 (2H,br.s), 1.61 (4H,br.s),

1.80-2.10 (2H,m), 2.88 (3H,s), 3.00-3.26 (2H,m),
3.40 (1H,br.s), 3.65 (1H,br.s), 4.22 (1H,br.s), 4.26 (1H,br.s),
4.41 (1H,br.s), 4.67 (1H,d,J=15.6Hz), 7.14 (1H,s),
7.28 (1H,d,J=8.7Hz), 7.37 (1H,d,J=8.7Hz), 7.84 (1H,s),
5 8.13 (1H,br.s), 8.33-8.52 (1H,m), 11.51 (1H,br.s),
11.86 (1H,s).

MS (ESI) m/z: 515 (M⁺).

[Example 12]

N-((1R*,2S*)-2-{[(5-Ethynylindol-2-yl)carbonyl]amino}-
10 cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridine-2-carboxamide hydrochloride:

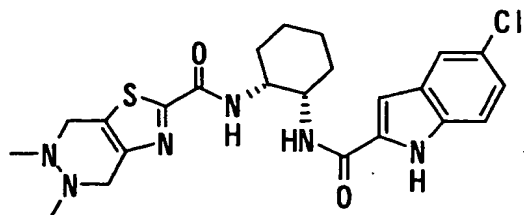


Triethylamine (6 ml), N,N-dimethylformamide (5 ml),
trimethylsilylacetylene (0.250 ml) and palladium acetate
15 (20 mg) were added to a tetrahydrofuran solution (2 ml) of
the compound (300 mg) obtained in Example 11 and
triphenylphosphine (70 mg) at room temperature. After
stirring at 90°C for 2 hours, the reaction mixture was
allowed to cool to room temperature, and methylene
20 chloride (20 ml) and a saturated aqueous solution (30 ml)
of sodium hydrogencarbonate were added to conduct liquid
separation. The resultant water layer was extracted with
methylene chloride (3 x 10 ml), the organic layers were
combined and dried over anhydrous sodium sulfate, and the

solvent was distilled off under reduced pressure to obtain residue. The resultant residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:acetone:methanol = 10:10:1) to obtain colorless solids. This product was dissolved in methanol (6 ml), potassium carbonate (120 mg) was added, and the mixture was stirred for 1 hour. Methylene chloride (20 ml) and water (20 ml) were added to the reaction mixture to conduct liquid separation. The resultant water layer was extracted with methylene chloride (2 x 15 ml), the organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:acetone:methanol = 10:10:1) and dissolved in water-methanol-methylene chloride. The resultant solution was then concentrated to obtain the title compound (72 mg).
¹H-NMR (CDCl₃) δ: 1.50-2.25(8H,m), 2.53(3H,s), 2.85(2H,br.s), 2.93(2H,br.s), 3.01(1H,s), 3.74(1H,d,J=14.1Hz), 3.77(1H,d,J=14.1Hz), 4.21(1H,br.s), 4.45(1H,br.s), 6.91(1H,s), 7.25-7.42(2H,m), 7.61(1H,br.s), 7.80-7.97(2H,m), 9.72(1H,s).
MS (FAB) m/z: 462(M+H)⁺.

[Example 13]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]-pyridazine-2-carboxamide hydrochloride:



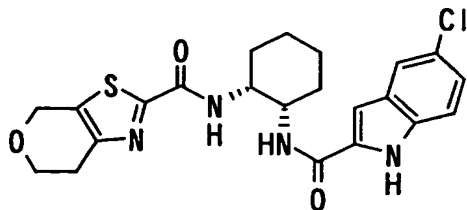
The title compound was obtained from the compound
 obtained in Referential Example 71 and the compound
 obtained in Referential Example 51 in a similar manner to
 5 Example 2.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.35-1.50 (2H,m), 1.50-1.75 (4H,m), 1.80-
 2.10 (2H,m), 2.70 (3H,br.s), 2.79 (3H,br.s),
 4.10-4.70 (6H,m), 7.10-7.27 (2H,m), 7.41 (1H,d,J=8.8Hz),
 7.70 (1H,s), 8.12 (1H,d,J=6.8Hz), 8.47 (1H,d,J=7.6Hz),
 10 11.85 (1H,s).

MS (FAB) m/z : 487 ($\text{M}+\text{H}$) $^+$.

[Example 14]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-
 cyclohexyl)-6,7-dihydro-4H-pyrano[4,3-d]thiazole-2-
 15 carboxamide:



The title compound was obtained from the compound
 obtained in Referential Example 71 and the compound
 obtained in Referential Example 26 in a similar manner to

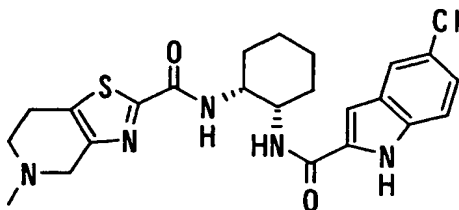
Example 2.

¹H-NMR (DMSO-d₆) δ: 1.36-1.72 (6H,m), 1.90-2.10 (2H,m), 2.80-2.87 (2H,m), 3.93 (2H,t, J=5.6Hz), 4.20-4.32 (2H,m), 4.81 (2H,s), 7.12 (1H,s), 7.15 (1H,dd, J=8.8,2.0Hz), 5 7.41 (1H,d, J=8.8Hz), 7.67 (1H,d, J=1.7Hz), 8.11 (1H,d, J=6.6Hz), 8.36 (1H,d, J=8.3Hz), 11.78 (1H,s).

MS (FAB) m/z: 459 (M+H)⁺.

[Example 15]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-
10 cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]-
pyridine-2-carboxamide hydrochloride:



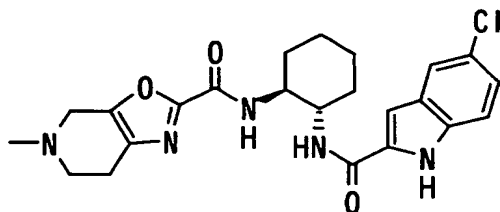
The title compound was obtained from the compound
obtained in Referential Example 71 and the compound
15 obtained in Referential Example 29 in a similar manner to
Example 2.

¹H-NMR (DMSO-d₆) δ: 1.32-1.74 (6H,m), 1.82-2.10 (2H,m), 2.92 (3H,s), 3.12-3.50 (3H,m), 3.69 (1H,br.s), 4.13-4.39 (3H,m), 4.51 (1H,br.s), 7.10-7.19 (2H,m), 20 7.41 (1H,d, J=8.6Hz), 7.68 (1H,s), 8.10 (1H,br.s), 8.40 (1H,br.s), 11.41 (1H,br.s), 11.87 (1H,s).

MS (FAB) m/z: 472 (M+H)⁺.

[Example 16]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



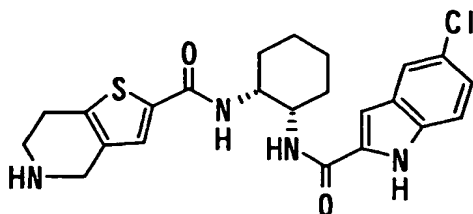
5 The title compound was obtained from the compound obtained in Referential Example 69 and the compound obtained in Referential Example 21 in a similar manner to Example 2.

¹H-NMR (DMSO-d₆) δ: 1.23-1.39(2H,m), 1.40-1.81(4H,m), 1.82-
10 1.98(2H,m), 2.60-3.00(5H,m), 3.20-3.70(2H,m),
3.87-3.96(1H,m), 3.98-4.10(1H,m), 4.12-4.70(2H,m),
7.04(1H,d,J=1.5Hz), 7.12(1H,dd,J=8.8,2.0Hz),
7.38(1H,d,J=8.8Hz), 7.65(1H,d,J=2.0Hz), 8.33(1H,d,J=8.6Hz),
8.72(1H,d,J=8.6Hz), 11.61(1H,br.s), 11.72(1H,s).

15 MS (FAB) m/z: 456(M+H)⁺.

[Example 17]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide hydrochloride:



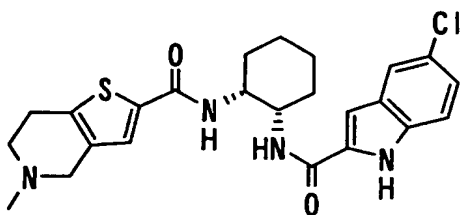
The title compound was obtained by condensing the compound obtained in Referential Example 71 with 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine-2-
 5 carboxylic acid (WO94/21599) and treating the formed product with hydrochloric acid to deprotect in a similar manner to Example 2.

¹H-NMR (DMSO-d₆) δ: 1.42(2H,br.s), 1.56-1.76(4H,m),
 1.98-2.11(2H,m), 3.04(2H,br.s), 3.32-3.45(2H,m),
 10 4.15(3H,br.s), 4.26(1H,br.s), 7.14(1H,dd,J=8.8,2.0Hz),
 7.23(1H,s), 7.41(1H,d,J=8.8Hz), 7.62(1H,s), 7.77(1H,s),
 8.18-8.30(2H,m), 9.42(2H,br.s), 11.92(1H,s).

MS (FAB) m/z: 457(M+H)⁺.

[Example 18]

15 N-((1R*,2S*)-2-(((5-Chloroindol-2-yl)carbonyl)amino)-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine-2-carboxamide hydrochloride:



The compound (171 mg) obtained in Example 17 was

suspended in methylene chloride (10 ml), and triethylamine (0.104 ml) was added to stir the mixture at room temperature for 10 minutes. After acetic acid (0.059 ml) was added to the reaction mixture, a 35% aqueous formaldehyde solution (0.070 ml) and sodium triacetoxymethylborohydride (118 mg) were added, and the mixture was stirred at room temperature for 30 minutes. After a 1N aqueous solution (3 ml) of sodium hydroxide was added to the reaction mixture, water was added to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was then distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 50:3) to obtain a colorless foamy substance. This substance was suspended in 1N hydrochloric acid, and the suspension was concentrated under reduced pressure to obtain the title compound (85 mg).

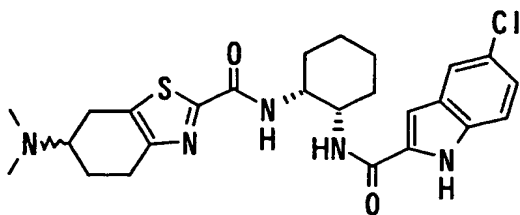
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.40 (2H, br.s), 1.50-1.71 (4H, m), 1.97-2.05 (2H, m), 2.87 (3H, s), 2.98-3.20 (1H, m), 3.30-3.38 (2H, m), 3.54-3.70 (1H, m), 4.05-4.42 (4H, m), 7.14 (1H, d, $J=8.6\text{Hz}$), 7.23 (1H, s), 7.40 (1H, d, $J=8.6\text{Hz}$), 7.63 (1H, s), 7.77 (1H, s), 8.17-8.27 (2H, m), 10.83 (1H, br.s), 11.92 (1H, s).

MS (FAB) m/z : 471 ($\text{M}+\text{H}$) $^+$.

[Example 19]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-6-(dimethylamino)-4,5,6,7-

tetrahydrobenzothiazole-2-carboxamide hydrochloride:



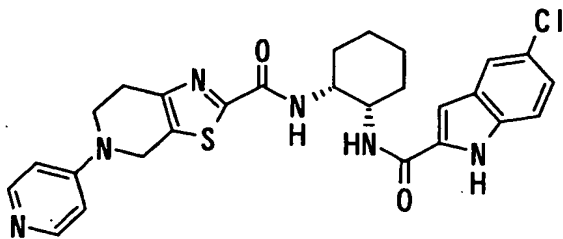
The title compound was obtained from the compound
obtained in Referential Example 71 and the compound
5 obtained in Referential Example 31 in a similar manner to
Example 2.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.44 (2H, br. s), 1.52-1.68 (4H, m), 1.87-
2.08 (3H, m), 2.30-2.40 (1H, m), 2.65-2.75 (1H, m), 2.77 (6H, s),
2.95-3.17 (2H, m), 3.30-3.70 (2H, m), 4.15-4.30 (2H, m), 7.10-
10 7.20 (2H, m), 7.41 (1H, d, $J=8.6\text{Hz}$), 7.69 (1H, s),
8.11 (1H, d, $J=5.1\text{Hz}$), 8.34 (1H, d, $J=8.1\text{Hz}$), 10.95 (1H, br. s),
11.83 (1H, s).

MS (FAB) m/z : 500 ($\text{M}+\text{H}$) $^+$.

[Example 20]

15 N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-
cyclohexyl)-5-(pyridin-4-yl)-4,5,6,7-tetrahydrothiazolo-
[5,4-c]pyridine-2-carboxamide hydrochloride:



After n-butyllithium (1.60N hexane solution, 0.704

ml) was added dropwise to a solution of the compound (204 mg) obtained in Referential Example 24 in tetrahydrofuran (3 ml) at -78°C, the mixture was stirred at 0°C for 30 minutes. After the reaction mixture was cooled to -78°C again, it was warmed to room temperature in 20 minutes while blowing carbon dioxide, and the reaction mixture was concentrated under reduced pressure. The compound (400 mg) obtained in Referential Example 71, 1-hydroxy-benzotriazole monohydrate (254 mg), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (360 mg) and isopropylamine (0.491 ml) were added to a solution of the resultant residue in N,N-dimethylformamide (6 ml) at room temperature. After stirring for 3 days, the reaction mixture was concentrated under reduced pressure, and methylene chloride (30 ml), a saturated aqueous solution (100 ml) of sodium hydrogencarbonate and water (100 ml) were added to the residue to conduct liquid separation. The resultant water layer was extracted with methylene chloride (4 x 15 ml), the organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1 → 10:1) and dissolved in 1N hydrochloric acid-methanol-methylene chloride. The resultant solution was then concentrated to obtain the title compound (245 mg).

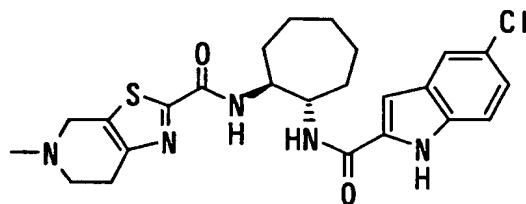
¹H-NMR (DMSO-d₆) δ: 1.42(2H,br.s), 1.60(4H,br.s),

1.84-1.94 (1H,m), 1.94-2.08 (1H,m), 2.97 (2H,br.s),
 3.97-4.13 (2H,m), 4.19 (1H,br.s), 4.27 (1H,br.s), 5.03 (2H,s),
 7.13 (1H,br.s), 7.16 (1H,dd,J=8.8,2.0Hz), 7.32 (2H,br.s),
 7.40 (1H,d,J=8.8Hz), 7.68 (1H,d,J=2.0Hz),
 5 8.15 (1H,br,J=7.3Hz), 8.31 (2H,d,J=5.9Hz),
 8.39 (1H,d,J=8.1Hz), 11.90 (1H,s), 14.03 (1H,br.s).

MS (ESI) m/z: 535 (M+H)⁺.

[Example 21]

N-((1R*,2R*)-2-[[(5-Chloroindol-2-yl)carbonyl]amino]-
 10 cycloheptyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
 pyridine-2-carboxamide hydrochloride:



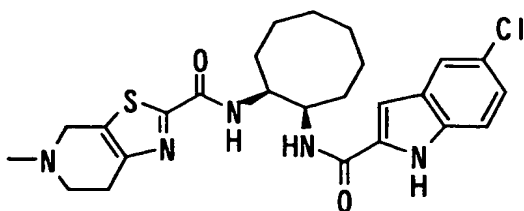
The title compound was obtained from the compound
 obtained in Referential Example 74 and the compound
 15 obtained in Referential Example 10 in a similar manner to
 Example 2.

¹H-NMR (DMSO-d₆) δ: 1.51-1.55 (4H,m), 1.75-1.80 (6H,m),
 2.88 (3H,s), 3.12 (1H,br.s), 3.35-3.63 (4H,m),
 4.10-4.13 (1H,m), 4.29-4.61 (2H,m), 7.06 (1H,s),
 20 7.14 (1H,dd,J=8.8,2.0Hz), 7.39 (1H,d,J=8.8Hz),
 7.67 (1H,d,J=2.0Hz), 8.46 (1H,d,J=8.3Hz), 8.77 (1H,d,J=8.3Hz),
 11.21-11.35 (1H,m), 11.71 (1H,s).

MS (ESI) m/z: 486 (M+H)⁺.

[Example 22]

N-((1R*,2S*)-2-([(5-Chloroindol-2-yl)carbonyl]amino)-cyclooctyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



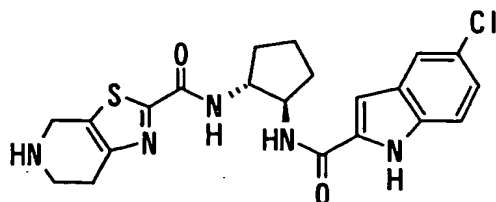
5

The title compound was obtained from the compound obtained in Referential Example 78 and the compound obtained in Referential Example 10 in a similar manner to Example 2.

- 10 $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.61-2.06 (12H,m), 2.90 (3H,s),
3.08-3.17 (2H,m), 3.43-3.45 (1H,br.s), 3.67 (1H,br.s),
4.43 (3H,br.s), 4.67 (1H,br.s), 7.16-7.18 (2H,m),
7.42 (1H,d,J=8.8Hz), 7.70 (1H,s), 8.24 (1H,br.s),
8.58 (1H,d,J=8.3Hz), 11.43,11.63 (1H,each br.s), 11.80 (1H,s).
- 15 MS (ESI) m/z: 500 (M+H) $^+$.

[Example 23]

N-((1R*,2R*)-2-([(5-Chloroindol-2-yl)carbonyl]amino)-cyclopentyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



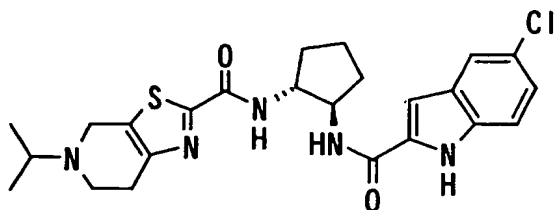
The title compound was obtained by treating a product obtained by the reaction of the compound obtained in Referential Example 63 with the compound obtained in Referential Example 34 with hydrochloric acid in a similar manner to Example 2.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.60-1.82 (4H,m), 1.91-2.15 (2H,m), 3.08 (2H,s), 3.37-3.49 (2H,m), 4.28-4.56 (4H,m), 7.13 (1H,s), 7.15 (1H,d,J=8.8Hz), 7.40 (1H,d,J=8.8Hz), 7.69 (1H,s), 8.61 (1H,d,J=8.3Hz), 8.88 (1H,d,J=8.3Hz), 10.05 (2H,br.s), 11.82 (1H,s).

MS (FAB) m/z : 444 ($\text{M}+\text{H}$) $^+$.

[Example 24]

N-((1R*,2R*)-2-{{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclopentyl)-5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (30 mg) obtained in Example 23 was suspended in methylene chloride (20 ml), and triethylamine

(260 μ l) was added to stir the mixture at room temperature for 15 minutes. Acetic acid (179 μ l) and acetone (920 μ l) were added to the reaction mixture, and the resultant mixture was stirred at room temperature for 2 minutes.

5 Sodium triacetoxyborohydride (796 mg) was added to the reaction mixture to stir them at room temperature for 5 hours. A 1N aqueous solution (10 ml) of sodium hydroxide was added to the reaction mixture to conduct liquid separation. The resultant organic layer was dried over

10 anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 100:3) to obtain a colorless foamy substance. This product was dissolved in methylene

15 chloride, and a 1N ethanol solution (1 ml) of hydrochloric acid was added. The solution was concentrated under reduced pressure to obtain the title compound (205 mg).

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.27-1.39(6H,m), 1.58-1.80(4H,m), 1.95-2.10(2H,m), 3.00-3.12(1H,m), 3.25-3.45(2H,m),

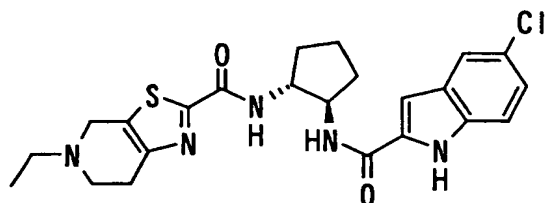
20 3.59-3.77(2H,m), 4.25-4.39(1H,m), 4.40-4.55(2H,m), 4.57-4.65(1H,m), 7.10(1H,s), 7.14(1H,d,J=8.8Hz), 7.38(1H,d,J=8.8Hz), 7.68(1H,s), 8.56(1H,d,J=8.8Hz), 8.90(1H,d,J=8.8Hz), 11.39(1H,br.s), 11.76(0.5H,s), 11.80(0.5H,s).

25 MS (FAB) m/z : 486(M+H) $^+$.

[Example 25]

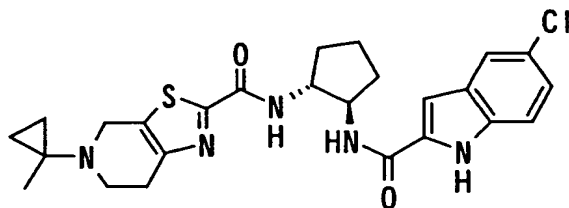
N-((1R*,2R*)-2-{{(5-Chloroindol-2-yl)carbonyl}amino})-

cyclopentyl)-5-ethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridine-2-carboxamide hydrochloride:



The compound (500 mg) obtained in Example 23 was
5 dissolved in N,N-dimethylformamide (10 ml), and
triethylamine (576 μ l) and ethyl iodide (329 μ l) were
added to stir the mixture overnight at room temperature.
The reaction mixture was concentrated under reduced
pressure, and water was added to the residue to collect
10 insoluble matter by filtration. This product was purified
by column chromatography on silica gel (methylene
chloride:methanol = 100:3) to obtain a pale brown foamy
substance. This substance was suspended in 1N hydrochloric
acid, and the suspension was concentrated under reduced
15 pressure to obtain the title compound (180 mg).
 $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.32 (3H,t,J=7.1Hz), 1.60-1.80 (4H,m),
1.96-2.10 (2H,m), 3.20-3.39 (5H,m), 3.70-3.80 (1H,m),
4.26-4.58 (3H,m), 4.68-4.79 (1H,m), 7.11 (1H,s),
7.15 (1H,dd,J=8.8,2.0Hz), 7.39 (1H,d,J=8.8Hz),
20 7.69 (1H,d,J=1.5Hz), 8.55 (1H,d,J=8.5Hz), 8.92 (1H,d,J=8.5Hz),
11.38 (1H,br.s), 11.70-11.80 (1H,m).
MS (FAB) m/z: 472 (M+H) $^+$.
[Example 26]

N-((1R*,2R*)-2-[[(5-Chloroindol-2-yl) carbonyl] amino]-cyclopentyl)-5-(1-methylcyclopropyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



5

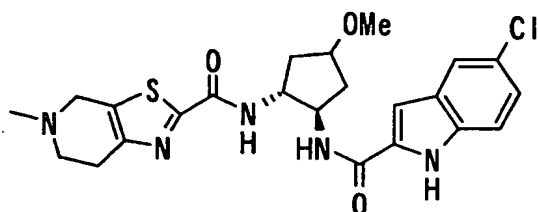
The title compound was obtained from the compound obtained in Referential Example 63 and the compound obtained in Referential Example 39 in a similar manner to Example 2.

10 ¹H-NMR (DMSO-d₆) δ: 0.81(2H,br.s), 1.20-1.55(5H,br), 1.55-1.80(4H,m), 1.95-2.12(2H,m), 3.05-3.40(2H,br), 3.60-3.80(2H,br), 4.25-4.80(4H,m), 7.10(1H,s), 7.16(1H,d,J=8.8Hz), 7.39(1H,d,J=8.8Hz), 7.69(1H,s), 8.53(1H,d,J=8.6Hz), 8.85-8.95(1H,m), 10.60-10.90(1H,br),
15 11.73(1H,br.s).

MS (FAB) m/z: 498 (M+H)⁺.

[Example 27]

N-((1R*,2R*)-2-[[(5-Chloroindol-2-yl) carbonyl] amino]-4-methoxycyclopentyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-
20 [5,4-c]pyridine-2-carboxamide hydrochloride (Stereoisomer A and Stereoisomer B):



A mixture of the title compounds, i.e., Stereoisomer A and Stereoisomer B was synthesized by condensing the compound (mixture of 4-position stereoisomers) (268 mg) obtained in Referential Example 82 with the compound obtained in Referential Example 10 in a similar manner to Example 2. The isomers were isolated by column chromatography on silica gel and then converted into hydrochlorides to obtain the title compounds [Stereoisomer A (75 mg) and Stereoisomer B (70 mg)].

Stereoisomer A:

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.70-2.15(4H,m), 2.90(3H,s), 3.00-3.90(8H,m), 4.10-4.80(4H,m), 7.08(1H,s), 7.16(1H,d,J=8.8Hz), 7.38(1H,d,J=8.8Hz), 7.69(1H,s), 8.56(1H,d,J=8.8Hz), 8.88(1H,d,J=8.3Hz), 10.96(1H,br.s), 11.75(1H,br.s).

MS (FAB) m/z : 488($\text{M}+\text{H}$) $^+$.

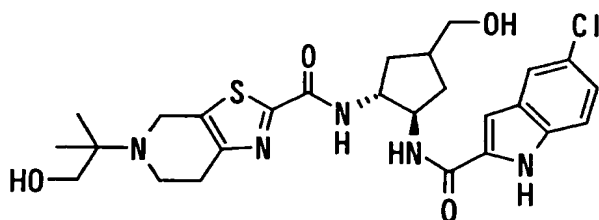
Stereoisomer B:

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.60-2.10(4H,m), 2.89(3H,s), 3.00-3.70(7H,m), 3.70-3.90(1H,m), 4.20-4.80(4H,m), 7.05-7.20(2H,m), 7.38(1H,d,J=8.8Hz), 7.68(1H,s), 8.59(1H,d,J=8.3Hz), 8.90(1H,d,J=8.5Hz), 11.26(1H,br.s), 11.74(1H,br.s).

MS (FAB) m/z: 488 (M+H)⁺.

[Example 28]

N-[(1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-(hydroxymethyl)cyclopentyl]-5-(1,1-dimethyl-2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride (Stereoisomer A):



1) Stereoisomers A and B of N-[(1R*,2R*)-4-[(benzyloxy)methyl]-2-{(5-chloroindol-2-yl)carbonyl}amino)cyclopentyl]-5-(2-{[tert-butyl(diphenyl)silyl]oxy}-1,1-dimethylethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide were obtained from the compound obtained in Referential Example 85 and the compound obtained in Referential Example 42 in a similar manner to Example 2.

Stereoisomer A:

¹H-NMR (CDCl₃) δ: 1.05 (9H, s), 1.168, 1.171 (6H, each s), 1.53-1.61 (1H, m), 1.76-1.88 (1H, m), 2.30-2.37 (2H, m), 2.78-2.79 (2H, m), 2.87-2.90 (1H, m), 2.96-3.00 (1H, m), 3.37-3.47 (2H, m), 3.58 (2H, s), 3.96 (1H, q, J=13.1 Hz), 4.41-4.45 (1H, m), 4.51-4.57 (2H, m), 6.88 (1H, d, J=1.5 Hz), 7.17 (1H, dd, J=8.8, 2.0 Hz), 7.23-7.43 (12H, m), 7.52 (1H, d, J=7.6 Hz), 9.37 (1H, br. s).

Stereoisomer B:

¹H-NMR (CDCl₃) δ: 1.05 (9H, s), 1.17 (6H, s), 1.43-1.47 (1H, m),
1.85-1.88 (1H, m), 2.09-2.14 (1H, m), 2.58-2.63 (1H, m),
2.78-2.79 (2H, m), 2.86-2.90 (1H, m), 2.96-3.00 (1H, m),
5 3.38-3.46 (2H, m), 3.59 (2H, s), 3.95 (1H, q, J=13.3 Hz),
4.15-4.20 (1H, m), 4.45-4.56 (3H, m), 6.74 (1H, d, J=2.0 Hz),
7.16 (1H, dd, J=8.8, 2.0 Hz), 7.27-7.43 (12H, m),
7.57 (1H, d, J=2.0 Hz), 9.48 (1H, br. s).

2) The above Stereoisomer A (288 mg) was suspended
10 in methylene chloride (20 ml), and dimethyl sulfide (1.15
ml) and anhydrous aluminum chloride (350 mg) were added to
stir the mixture at room temperature for 1 hour. A 1N
aqueous solution (10 ml) of sodium hydroxide was added to
the reaction mixture, and the mixture was extracted with
15 methylene chloride. The resultant organic layer was dried
over anhydrous sodium sulfate. The solvent was distilled
off under reduced pressure, and the residue was purified
by column chromatography on silica gel (methylene
chloride:methanol = 9:1) to obtain 5-(2-[[tert-
20 butyl(diphenyl)silyl]oxy]-1,1-dimethylethyl)-N-[(1R*,2R*)-
2-[[(5-Chloroindol-2-yl) carbonyl] amino]-4-
(hydroxymethyl)cyclopentyl]-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
(Stereoisomer A) (184 mg).

25 ¹H-NMR (CDCl₃) δ: 1.04 (9H, s), 1.15 (6H, s), 1.54-1.62 (1H, m),
1.73-1.81 (1H, m), 1.99-2.25 (2H, m), 2.34-2.38 (2H, m),
2.67-2.85 (3H, m), 2.92-2.97 (1H, m), 3.48-3.62 (4H, m),

3.93(1H,q,J=15.6Hz), 4.20-4.28(1H,m), 4.47-4.56(1H,m),
6.89(1H,s), 7.11-7.18(1H,m), 7.24-7.27(1H,m), 7.32-
7.43(6H,m), 7.54(1H,d,J=1.7Hz), 7.63(4H,dd,J=7.8,1.5Hz),
7.90-7.92(2H,m), 10.13(1H,br.s).

5 MS (FAB) m/z: 784(M+H)⁺.

3) Stereoisomer A (180 mg) obtained in the step 2) described above was dissolved in a 1N tetrahydrofuran solution (2 ml) of tetrabutylammonium fluoride, and the solution was stirred overnight at room temperature.

10 Methylene chloride, a 1N aqueous solution of sodium hydroxide and sodium chloride were added to the reaction mixture to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the
15 residue was purified by column chromatography on silica gel (methylene chloride:methanol = 19:1). The thus-obtained powder was dissolved in methanol, and a 1N ethanol solution (229 μ l) of hydrochloric acid was added, to which ethyl acetate was added. The solvent was
20 concentrated under reduced pressure to obtain the title compound (63 mg).

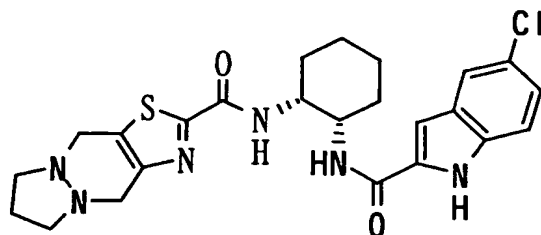
¹H-NMR (DMSO-d₆) δ : 1.33-1.50(8H,m), 1.70-1.91(2H,m), 2.07-
2.14(1H,m), 2.23-2.24(1H,m), 3.04-3.10(1H,m),
3.27-3.44(4H,m), 3.57-3.70(2H,m), 3.92-3.95(1H,m),
25 4.29-4.72(4H,m), 5.81(1H,br.s), 7.11(1H,s),
7.15(1H,dd,J=8.6,2.0Hz), 7.39(1H,d,J=8.6Hz),
7.68(1H,d,J=2.0Hz), 8.53-8.56(1H,m), 8.83(1H,d,J=8.3Hz),

10.36(1H,br.s), 11.75,11.77(1H,each s).

MS (ESI) m/z: 546(M+H)⁺.

[Example 29]

N-((1R*,2S*)-2-[[(5-Chloroindol-2-yl)carbonyl]amino]-
5 cyclohexyl)-4,7,8,10-tetrahydro-6H-pyrazolo[1,2-a]-
thiazolo[4,5-d]pyridazine-2-carboxamide hydrochloride:



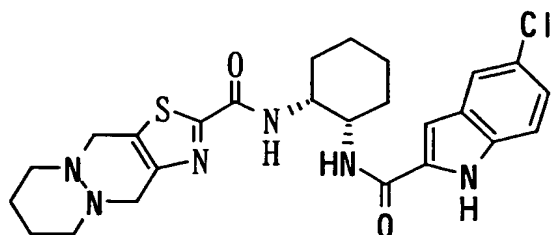
The title compound was obtained from the compound
obtained in Referential Example 71 and the compound
10 obtained in Referential Example 44 in a similar manner to
Example 2.

¹H-NMR (DMSO-d₆) δ: 1.35-1.50(2H,m), 1.61(4H,br.s), 1.80-
2.00(2H,m), 2.27(2H,br.s), 2.80-4.80(10H,m),
7.14(1H,d,J=1.5Hz), 7.17(1H,dd,J=8.5,2.0Hz),
15 7.41(1H,d,J=8.5Hz), 7.70(1H,d,J=2.0Hz), 8.09(1H,d,J=7.3Hz),
8.44(1H,br.s), 11.81(1H,br.s).

MS (FAB) m/z: 499(M+H)⁺.

[Example 30]

N-((1R*,2S*)-2-[[(5-Chloroindol-2-yl)carbonyl]amino]-
20 cyclohexyl)-4,6,7,8,9,11-hexahydropyridazino[1,2-a]-
thiazolo[4,5-d]pyridazine-2-carboxamide hydrochloride:



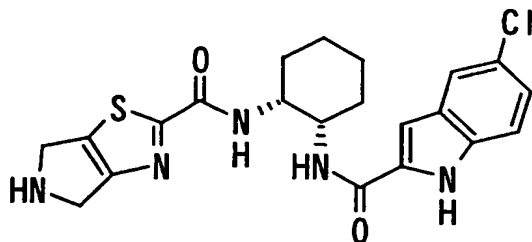
The title compound was obtained from the compound obtained in Referential Example 46 and the compound obtained in Referential Example 71 in a similar manner to
 5 Example 2.

¹H-NMR (DMSO-d₆) δ: 1.35-1.55(2H,m), 1.55-2.10(10H,m), 2.80-4.80(10H,m), 7.10-7.25(2H,m), 7.42(1H,d,J=8.8Hz), 7.72(1H,d,J=1.7Hz), 8.12(1H,br.s), 8.41(1H,br.s), 11.83(1H,br.s).

10 MS (FAB) m/z: 513(M+H)⁺.

[Example 31]

5-Chloro-N-((1R*,2S*)-2-[(5,6-dihydro-4H-pyrrolo[3,4-d]-thiazol-2-ylcarbonyl)amino]cyclohexyl)indole-2-carboxamide hydrochloride:



15

The compound (171 mg) obtained in Referential Example 33 was dissolved in diethyl ether (5 ml) in an argon atmosphere, and the solution was cooled to -78°C, to which n-butyllithium (1.60N hexane solution, 385 μl) was

added dropwise. After the reaction mixture was stirred for 10 minutes at -78°C , and carbon dioxide was blown into the reaction mixture for 20 minutes, it was warmed to room temperature. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in N,N-dimethylformamide (10 ml). To the solution, were added the compound (184 mg) obtained in Referential Example 71, 1-hydroxybenzotriazole monohydrate (76 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (215 mg). The resultant mixture was stirred for 3 days. The reaction mixture was concentrated, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (methanol:methylene chloride = 3:97). After an ethanol solution (5 ml) of hydrochloric acid was added to the thus-obtained product, the mixture was stirred at room temperature for 1 hour, and the reaction mixture was concentrated. Ethyl acetate was added to the residue to solidify it. The resultant powder was collected by filtration to obtain the title compound (31 mg).

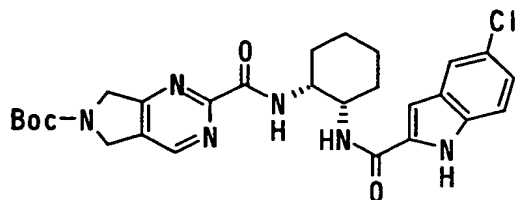
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.35-1.52 (2H,m), 1.55-1.80 (4H,m), 1.82-2.05 (2H,m), 4.22 (1H,br.s), 4.28 (1H,br.s), 4.38 (2H,s), 4.56 (2H,s), 7.14-7.20 (2H,m), 7.42 (1H,d,J=8.6Hz),

7.71(1H,d,J=1.7Hz), 8.10(1H,d,J=7.1Hz), 8.45(1H,d,J=7.8Hz),
10.10-10.50(2H,br), 11.83(1H,br.s).

MS (FAB) m/z: 444(M+H)⁺.

[Example 32]

5 tert-Butyl 2-{[(((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)amino]carbonyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate :



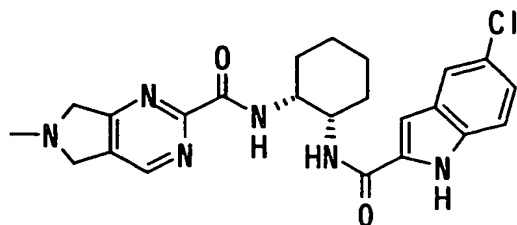
After the compound obtained in Referential Example
10 50 was hydrolyzed with lithium hydroxide, it was reacted with the compound obtained in Referential Example 71 in a similar manner to Example 2 to obtain the title compound.

¹H-NMR (CDCl₃) δ: 1.54(9H,s), 1.55-2.30(8H,m),
4.23(1H,br.s), 4.53(1H,br.s), 4.74-4.83(4H,m),
15 6.99(1H,d,J=1.5Hz), 7.19(1H,dd,J=8.8,2.1Hz),
7.34(1H,d,J=8.8Hz), 7.62(1H,d,J=2.1Hz), 8.11(1H,br.s),
8.48-8.53(1H,br), 8.70-8.76(1H,br), 9.60-9.70(1H,br).

MS (ESI) m/z: 539(M+H)⁺.

[Example 33]

20 N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-d]-pyrimidine-2-carboxamide hydrochloride:



Trifluoroacetic acid (1 ml) was added to a solution of the compound (34.0 mg) obtained in Example 32 dissolved in methylene chloride (1 ml) at room temperature, and the mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (1 ml), to which triethylamine (17.6 μ l), acetic acid (7.21 μ l), 35% formalin (8.13 μ l) and sodium triacetoxyborohydride (20.1 mg) were added at room temperature. The resultant mixture was stirred for 1 hour. Methylene chloride (10 ml) and saturated aqueous solution (10 ml) of sodium hydrogencarbonate were added to the reaction mixture to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 7:93). A 1N ethanol solution of hydrochloric acid and ethyl acetate were added to the product thus obtained to solidify it, and the resultant solids were collected by filtration to obtain the title compound (8.0 mg).

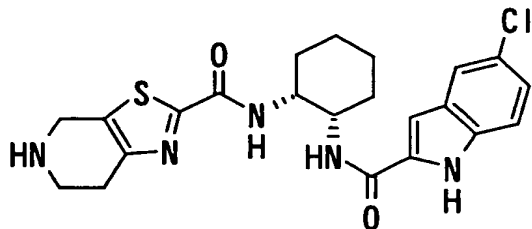
$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.40-1.55(2H,m), 1.55-1.75(4H,m), 1.80-

2.05 (2H,m), 2.98 (3H,br.s), 4.28 (2H,br.s), 4.65 (4H,br.s),
7.14-7.20 (2H,m), 7.41 (1H,d,J=8.8Hz), 7.69 (1H,d,J=2.0Hz),
8.17 (1H,d,J=6.9Hz), 8.65 (1H,d,J=8.3Hz), 8.93 (1H,s),
11.73 (1H,br.s), 11.82 (1H,br.s).

5 MS (FAB) m/z: 453 (M+H)⁺.

[Example 34]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-
cyclohexyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-
carboxamide hydrochloride:



10

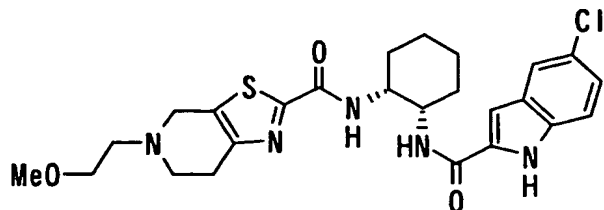
The title compound was obtained by treating a
product obtained by the reaction of the compound obtained
in Referential Example 71 with the compound obtained in
Referential Example 34 with hydrochloric acid in a similar
15 manner to Example 2.

¹H-NMR (DMSO-d₆) δ: 1.39-1.52 (2H,m), 1.62 (4H,br.s),
1.86-2.09 (2H,m), 3.03 (2H,br.s), 3.40-3.47 (2H,m), 4.17-
4.32 (2H,m), 4.44 (2H,s), 7.15 (1H,s),
7.17 (1H,dd,J=8.6,2.0Hz), 7.41 (1H,d,J=8.6Hz), 7.71 (1H,s),
20 8.10-8.15 (1H,m), 8.40-8.47 (1H,m), 9.69 (2H,br.s),
11.85 (1H,s).

MS (FAB) m/z: 458 (M+H)⁺.

[Example 35]

N-((1R*,2S*)-2-[[(5-Chloroindol-2-yl)carbonyl]amino]-cyclohexyl)-5-(2-methoxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



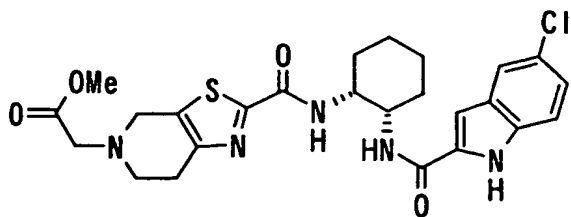
5 The title compound was obtained from the compound obtained in Example 34 and 2-methoxyethyl bromide in a similar manner to Example 25.

¹H-NMR (DMSO-d₆) δ: 1.44 (2H, br.s), 1.62 (4H, br.s), 1.85-2.10 (2H, m), 2.76-3.21 (6H, m), 3.28 (3H, s), 3.64 (2H, br.s),
10 4.00-4.52 (4H, m), 7.14 (1H, s), 7.17 (1H, dd, J=8.8, 2.0Hz), 7.41 (1H, d, J=8.8Hz), 7.70 (1H, d, J=2.0Hz), 8.08-8.20 (1H, m), 8.36-8.48 (1H, m), 11.84 (1H, s).

MS (FAB) m/z: 516 (M+H)⁺.

[Example 36]

15 Methyl 2-[2-[[((1R*,2S*)-2-[[(5-chloroindol-2-yl)-carbonyl]amino)cyclohexyl)amino]carbonyl]-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl]acetate hydrochloride:



The title compound was obtained from the compound

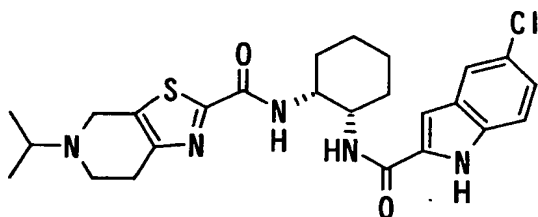
obtained in Example 34 and methyl bromoacetate in a similar manner to Example 25.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.52-1.98 (7H, m), 2.17 (1H, br. s), 2.87-3.10 (4H, m), 3.49 (2H, s), 3.76 (3H, s), 3.93 (1H, d, $J=15.4\text{Hz}$),
5 3.99 (1H, d, $J=15.4\text{Hz}$), 4.22 (1H, br. s), 4.45 (1H, br. s),
6.86 (1H, d, $J=1.2\text{Hz}$), 7.18 (1H, dd, $J=8.8, 2.0\text{Hz}$),
7.33 (1H, d, $J=8.8\text{Hz}$), 7.58-7.63 (2H, m), 7.87 (1H, br. s),
9.88 (1H, br. s).

MS (FAB) m/z : 530 ($M+H$) $^+$.

10 [Example 37]

N-((1R*,2S*)-2-[[(5-Chloroindol-2-yl) carbonyl] amino]-cyclohexyl)-5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



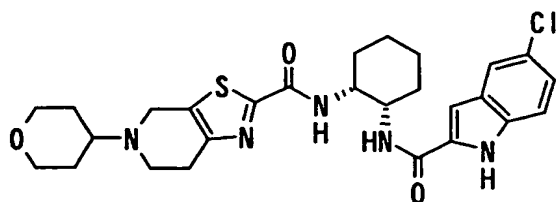
15 The title compound was obtained from the compound obtained in Example 34 and acetone in a similar manner to Example 24.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.18-1.73 (8H, m), 1.81-2.10 (2H, m), 2.97-3.16 (1H, m), 3.20-3.41 (2H, m), 3.52-3.80 (2H, m), 4.19-
20 4.31 (2H, m), 4.34-4.77 (2H, m), 7.17 (1H, s),
7.18 (1H, dd, $J=8.8, 2.0\text{Hz}$), 7.42 (1H, d, $J=8.8\text{Hz}$),
7.71 (1H, d, $J=2.0\text{Hz}$), 8.15 (1H, br. s), 8.28-8.51 (1H, m),
11.31 (1H, br. s), 11.86 (1H, s).

MS (FAB) m/z : 500 ($M+H$)⁺.

[Example 38]

N-((1R*,2S*)-2-[[(5-Chloroindol-2-yl) carbonyl] amino]-
cyclohexyl)-5-(tetrahydro-2H-pyran-4-yl)-4,5,6,7-
5 tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
hydrochloride:



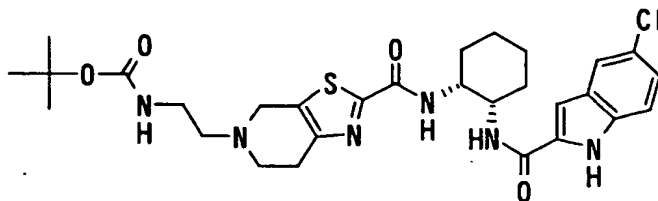
The title compound was obtained from the compound
obtained in Example 34 and tetrahydro-4H-pyran-4-one in a
10 similar manner to Example 24.

¹H-NMR (DMSO-d₆) δ : 1.30-3.56 (19H, m), 3.70-4.01 (3H, m),
4.17-4.30 (2H, m), 4.32-4.80 (1H, m), 7.15 (1H, s),
7.17 (1H, dd, $J=8.6, 2.0$ Hz), 7.41 (1H, d, $J=8.6$ Hz),
7.71 (1H, d, $J=2.0$ Hz), 8.14 (1H, br. s), 8.39 (1H, br. s),
15 11.84 (1H, s).

MS (FAB) m/z : 542 ($M+H$)⁺.

[Example 39]

tert-Butyl 2-[2-[[((1R*,2S*)-2-[[(5-chloroindol-2-
yl) carbonyl] amino] cyclohexyl) amino] carbonyl]-6,7-
20 dihydrothiazolo[5,4-c]pyridin-5(4H)-yl]ethylcarbamate:



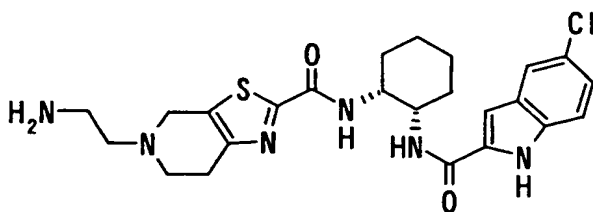
The title compound was obtained from the compound obtained in Example 34 and N-(tert-butoxycarbonyl)aminoacetoaldehyde (J. Org. Chem., 1988, Vol. 53, p.3457) in a similar manner to Example 24.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.44(9H,s), 1.54-1.98(7H,m), 2.10-2.20(1H,m), 2.74(2H,br.s), 2.92(4H,br.s), 3.34(2H,br.s), 3.84(2H,br.s), 4.21(1H,br.s), 4.45(1H,br.s), 6.86(1H,s), 7.19(1H,dd, $J=8.8, 2.0\text{Hz}$), 7.33(1H,d, $J=8.8\text{Hz}$), 7.57-7.63(2H,m), 7.81(1H,br.s), 9.66(1H,br.s).

10 MS (FAB) m/z : 601($\text{M}+\text{H}$) $^+$.

[Example 40]

5-(2-Aminoethyl)-N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)-carbonyl]amino}cyclohexyl)-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide hydrochloride:



15

The compound (450 mg) obtained in Example 39 was dissolved in methylene chloride (5 ml), and a saturated ethanol solution (30 ml) of hydrochloric acid was added to stir the mixture at room temperature for 1 minute. The reaction mixture was concentrated under reduced pressure, ethyl acetate was added to the residue, and solids deposited were collected by filtration to obtain the title compound (367 mg).

20 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.38-1.50(2H,m), 1.61(4H,br.s), 1.85-

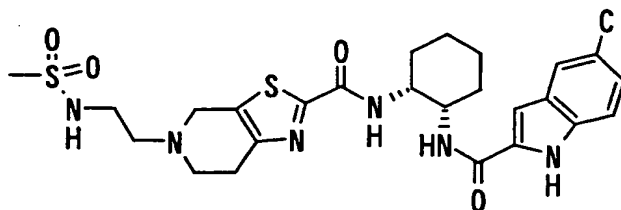
2.08 (2H, m), 3.00-4.62 (12H, m), 7.14 (1H, s),
7.16 (1H, dd, J=8.8, 2.0 Hz), 7.41 (1H, d, J=8.8 Hz),
7.69 (1H, d, J=2.0 Hz), 8.12 (1H, d, J=6.6 Hz), 8.15-8.68 (4H, m),
11.85 (1H, s).

5 MS (FAB) m/z: 501 (M+H)⁺.

[Example 41]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-
cyclohexyl)-5-{2-[(methanesulfonyl)amino]ethyl}-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide

10 hydrochloride:



The compound (110 mg) obtained in Example 40 was
dissolved in pyridine (3 ml), methanesulfonyl chloride (30
μl) was added, and the mixture was stirred overnight at
15 room temperature. The reaction mixture was concentrated
under reduced pressure, and a 85:15 mixed solvent of
methylene chloride and methanol, and water were added to
conduct liquid separation. The resultant organic layer was
dried over anhydrous sodium sulfate. The solvent was
20 distilled off under reduced pressure, and the residue was
purified by column chromatography on silica gel (methylene
chloride: methanol = 100:3) to obtain a pale yellow foamy
substance. This product was suspended in 1N hydrochloric
acid (0.3 ml), and the suspension was concentrated under

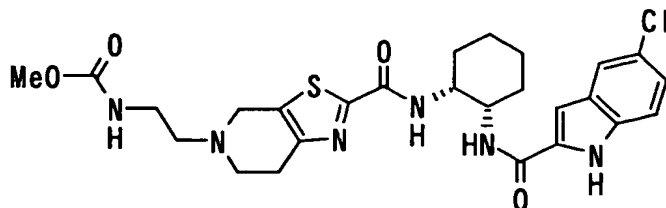
reduced pressure to obtain the title compound (63 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.38-1.50 (2H,m), 1.55-1.70 (4H,m), 1.86-2.05 (2H,m), 2.97 (3H,s), 3.02-3.25 (2H,m), 3.30-3.60 (5H,m), 3.78 (1H,br.s), 4.18-4.30 (2H,m), 4.45-4.86 (2H,m), 7.14 (1H,s), 7.16 (1H,dd, $J=8.8, 2.0\text{Hz}$), 7.40 (1H,d, $J=8.8\text{Hz}$), 7.41 (1H,br.s), 7.69 (1H,d, $J=2.0\text{Hz}$), 8.09 (1H,br.s), 8.43 (1H,br.s), 11.18 (1H,br.s), 11.82 (1H,s).

MS (FAB) m/z : 579 ($\text{M}+\text{H}$) $^+$.

[Example 42]

10 Methyl 2-[2-{{{(1R*,2S*)-2-[[5-chloroindol-2-yl]carbonyl]amino}cyclohexyl)amino]carbonyl}-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl]ethylcarbamate hydrochloride:



15 The compound (144 mg) obtained in Example 40 was dissolved in pyridine (3 ml), triethylamine (138 μl) was added, and the mixture was stirred at room temperature for 5 minutes. A solution prepared by adding triphosgene (49 mg) to tetrahydrofuran (1 ml) containing methanol (20 μl)
20 was added dropwise to this solution. After stirring for 1 hour, the reaction mixture was concentrated under reduced pressure, and the residue was dissolved in a 9:1 mixed solvent of methylene chloride and methanol. Water was

added to the solution to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column

5 chromatography on silica gel (methylene chloride: methanol = 100:3) to obtain a colorless foamy substance. This product was suspended in 1N hydrochloric acid (0.2 ml), and the suspension was concentrated under reduced pressure to obtain the title compound (60 mg).

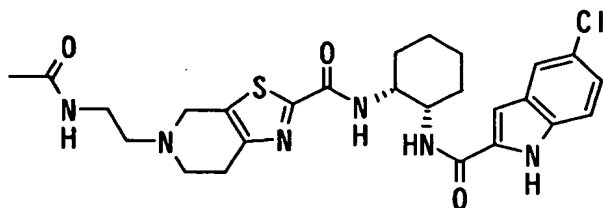
10 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.38-1.50 (2H,m), 1.61 (4H,br.s), 1.85-2.04 (2H,m), 2.80-3.49 (8H,m), 3.52 (3H,s), 3.62-4.91 (4H,m), 7.14 (1H,s), 7.16 (1H,dd, $J=8.8, 2.0\text{Hz}$), 7.37 (1H,br.s), 7.40 (1H,d, $J=8.8\text{Hz}$), 7.70 (1H,s), 8.11 (1H,d, $J=6.8\text{Hz}$), 8.40 (1H,br.s), 11.05 (1H,br.s), 11.82 (1H,br.s).

15 MS (FAB) m/z : 559 ($\text{M}+\text{H}$) $^+$.

[Example 43]

5-[2-(Acetylamino)ethyl]-N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide

20 hydrochloride:



The compound (90 mg) obtained in Example 40 was dissolved in N,N-dimethylformamide (3 ml), triethylamine

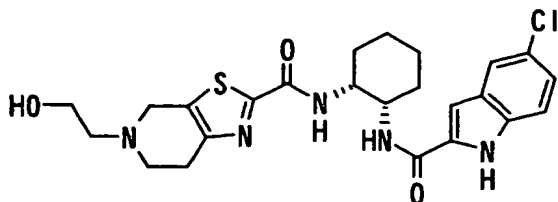
(65 μ l) and acetic anhydride (22 μ l) were added, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and methylene chloride and a 0.3N aqueous solution of sodium hydroxide were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride: methanol = 100:3) to obtain a colorless foamy substance. This product was suspended in 1N hydrochloric acid (0.3 ml), and the suspension was concentrated under reduced pressure to obtain the title compound (73 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.39-1.52(2H,m), 1.54-1.70(4H,m), 1.83(3H,s), 1.84-2.06(2H,m), 3.02-3.87(8H,m), 4.16-4.32(2H,m), 4.40-4.52(1H,m), 4.78-4.88(1H,m), 7.14(1H,s), 7.16(1H,d,J=8.6Hz), 7.40(1H,d,J=8.6Hz), 7.70(1H,s), 8.07-8.17(1H,m), 8.22-8.30(1H,m), 8.38-8.52(1H,m), 11.14(1H,br.s), 11.83(1H,s).

MS (FAB) m/z : 543($\text{M}+\text{H}$) $^+$.

[Example 44]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-(2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



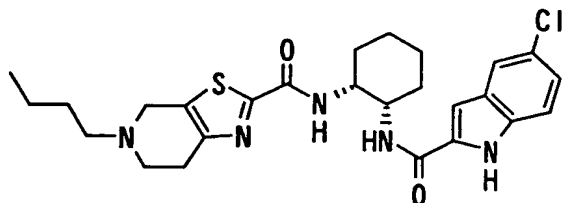
The title compound was obtained from the compound obtained in Example 34 and 2-bromoethanol in a similar manner to Example 25.

¹H-NMR (DMSO-d₆) δ: 1.37-1.69(6H,m), 1.86-2.03(2H,m), 2.54-2.61(2H,m), 2.75-2.86(4H,m), 3.52-3.59(2H,m), 3.75(2H,s), 4.47(1H,t,J=5.4Hz), 7.12(1H,s), 7.16(1H,dd,J=8.8,2.0Hz), 7.40(1H,d,J=8.8Hz), 7.70(1H,s), 8.05-8.13(1H,m), 8.28-8.35(1H,m), 11.78(1H,s).

MS (FAB) m/z: 502(M+H)⁺.

[Example 45]

5-Butyl-N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}cyclohexyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



15

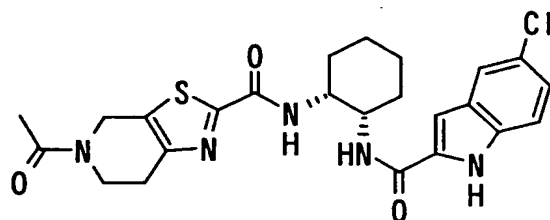
The title compound was obtained from the compound obtained in Example 34 and n-bromobutane in a similar manner to Example 25.

¹H-NMR (DMSO-d₆) δ: 0.88(3H,t,J=7.2Hz), 1.20-1.70(10H,m),

1.87-2.05 (2H,m), 2.55-3.40 (8H,m), 4.16-4.30 (2H,m),
7.13 (1H,s), 7.16 (1H,d,J=8.8Hz), 7.40 (1H,d,J=8.8Hz),
7.69 (1H,s), 8.05-8.14 (1H,m), 8.35 (1H,br.s), 11.81 (1H,s).
MS (FAB) m/z: 514 (M+H)⁺.

5 [Example 46]

5-Acetyl-N-((1R*,2S*)-2-[[(5-chloroindol-2-yl) carbonyl]-
amino]cyclohexyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridine-2-carboxamide:



10 The compound (100 mg) obtained in Example 34 was
dissolved in N,N-dimethylformamide (3 ml), triethylamine
(84 μ l) and acetic anhydride (29 μ l) were added, and the
mixture was stirred at room temperature for 3 hours. The
reaction mixture was concentrated under reduced pressure,
15 and methylene chloride and 1N hydrochloric acid were added
to the residue to conduct liquid separation. The resultant
organic layer was dried over anhydrous sodium sulfate. The
solvent was distilled off under reduced pressure, and the
residue was purified by column chromatography on silica
20 gel (methylene chloride: methanol = 100:3) to obtain the
title compound (86 mg).

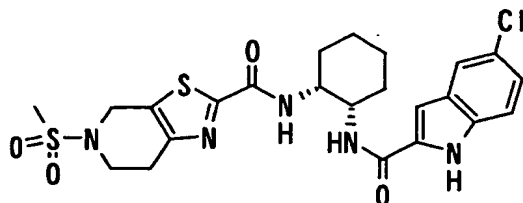
¹H-NMR (CDCl₃) δ : 1.52-1.85 (5H,m), 1.91 (2H,br.s), 2.10-
2.28 (4H,m), 2.77-3.00 (2H,m), 3.70-4.00 (2H,m), 4.19-

4.38 (1H,m), 4.45 (1H,br.s), 4.68-4.99 (2H,m), 6.85 (1H,s),
7.17-7.22 (1H,m), 7.30-7.39 (1H,m), 7.50-7.84 (3H,m), 9.72-
10.05 (1H,m).

MS (FAB) m/z: 500 (M+H)⁺.

5 [Example 47]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-
cyclohexyl)-5-(methylsulfonyl)-4,5,6,7-tetrahydro-
thiazolo[5,4-c]pyridine-2-carboxamide:



10 The compound (100 mg) obtained in Example 34 was
dissolved in pyridine (3 ml), triethylamine (168 μ l) and
methanesulfonyl chloride (48 μ l) were added, and the
mixture was stirred overnight at room temperature. The
reaction mixture was concentrated under reduced pressure,
15 and methylene chloride and 1N hydrochloric acid were added
to the residue to separate an organic layer. The resultant
organic layer was dried over anhydrous sodium sulfate. The
solvent was distilled off under reduced pressure, and the
residue was purified by column chromatography on silica
20 gel (methylene chloride:methanol = 100:1) to obtain the
title compound (79 mg).

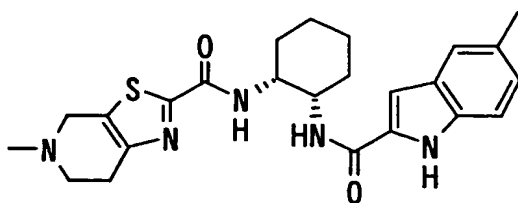
¹H-NMR (CDCl₃) δ : 1.50-1.82 (5H,m), 1.90 (2H,br.s),
2.13 (1H,br.s), 2.89 (3H,s), 2.91-2.98 (2H,m), 3.60-
3.70 (2H,m), 4.30 (1H,br.s), 4.44 (1H,br.s), 4.58 (2H,s),

6.87 (1H, s), 7.19 (1H, d, J=8.8 Hz), 7.34 (1H, d, J=8.8 Hz),
7.61 (3H, br. s), 9.91 (1H, br. s).

MS (FAB) m/z: 536 (M+H)⁺.

[Example 48]

5 5-Methyl-N-((1R*,2S*)-2-[[(5-methylindol-2-yl) carbonyl]-
amino)cyclohexyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridine-2-carboxamide hydrochloride:



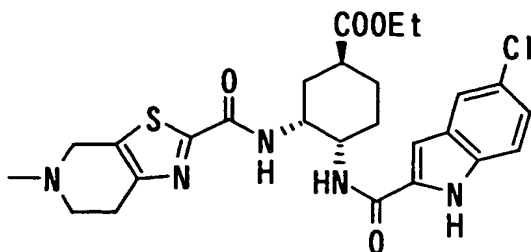
The title compound was obtained from the compound
10 obtained in Referential Example 67 and 5-methylindole-2-
carboxylic acid in a similar manner to Example 5.

¹H-NMR (DMSO-d₆) δ: 1.35-1.50 (2H, m), 1.50-1.80 (4H, m), 1.85-
2.07 (2H, m), 2.36 (3H, s), 2.88 (3H, s), 3.12 (2H, br. s),
3.53 (2H, br. s), 4.15-4.30 (2H, m), 4.30-4.80 (2H, br),
15 7.00 (1H, dd, J=8.4, 1.5 Hz), 7.05 (1H, d, J=1.5 Hz),
7.30 (1H, d, J=8.4 Hz), 7.38 (1H, s), 8.00 (1H, d, J=7.3 Hz),
8.43 (1H, br. s), 11.45 (1H, br. s), 11.49 (1H, br. s).

MS (FAB) m/z: 452 (M+H)⁺.

[Example 49]

20 Ethyl (1R*,3S*,4R*)-4-[[(5-chloroindol-2-yl) carbonyl]-
amino]-3-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridin-2-yl) carbonyl]amino)cyclohexanecarboxylate:



The compound (1.40 g) obtained in Referential Example 91 was suspended in ethanol (8 ml), and a saturated ethanol solution (10 ml) of hydrochloric acid was added at room temperature to stir the mixture for 12 hours. The solvent was distilled off under reduced pressure to obtain ethyl (1R*,3S*,4R*)-3-amino-4-{{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexanecarboxylate hydrochloride (1.25 g).

The title compound was obtained from the above-described product and the compound obtained in Referential Example 10 in a similar manner to Example 2.

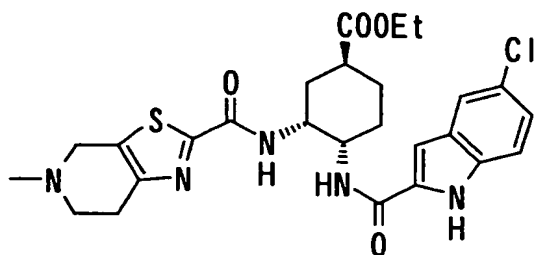
¹H-NMR (CDCl₃) δ: 1.29 (3H, t, J=7.1 Hz), 1.52-1.80 (2H, m), 2.03-2.37 (4H, m), 2.53 (3H, s), 2.57-2.71 (1H, m), 3.73 and 3.78 (total 1H, each d, J=14.4 Hz), 4.08-4.17 (1H, m), 4.18 (2H, q, J=7.2 Hz), 4.55-4.65 (1H, m), 6.85 (1H, br. s), 7.21 (1H, dd, J=8.8, 2.0 Hz), 7.33 (1H, d, J=8.8 Hz), 7.48 (1H, d, J=7.6 Hz), 7.63 (1H, d, J=2.0 Hz), 7.98 (1H, d, J=7.6 Hz), 9.30 (1H, s).

MS (ESI) m/z: 544 (M+H)⁺.

[Example 50]

Ethyl (1S,3R,4S)-4-{{[(5-chloroindol-2-yl)carbonyl]amino}-3-{{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]amino)cyclohexanecarboxylate:



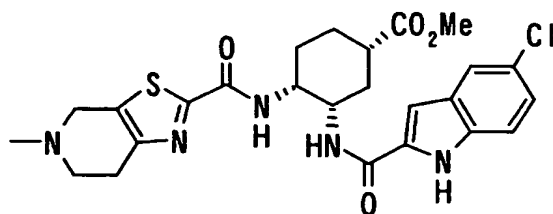
The compound (4.2 g) obtained in Referential Example 97 was suspended in ethanol (25 ml), and a saturated ethanol solution (55 ml) of hydrochloric acid was added at room temperature to stir the mixture for 11 hours. The solvent was distilled off under reduced pressure to obtain colorless solids (4.15 g).

This product (4.15 g) was dissolved in N,N-dimethylformamide (40 ml), and the compound (2.86 g) obtained in Referential Example 10, 1-hydroxybenzotriazole monohydrate (1.72 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.15 g) were added to this solution at room temperature to stir the mixture for 39 hours. The reaction mixture was concentrated under reduced pressure, and water was added to the residue to conduct extraction with chloroform. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (chloroform:methanol = 100:1) to obtain the title compound (1.71 g).

$[\alpha]_D -94^\circ$ (C=1.0, chloroform).

[Example 51]

Methyl (1R*,3R*,4S*)-3-{[(5-chloroindol-2-yl)carbonyl]-
amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
5 pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:



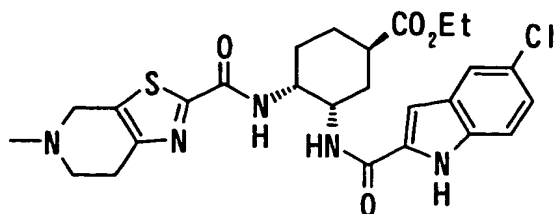
The title compound was obtained by treating the
compound obtained in Referential Example 107 with an
ethanol solution of hydrochloric acid and then condensing
10 this compound with the compound obtained in Referential
Example 10 in a similar manner to Example 49.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.55-1.80 (3H,m), 1.80-2.20 (3H,m), 2.60-
2.75 (1H,m), 2.92 (3H,s), 3.15-3.30 (1H,m), 3.30-3.50 (4H,m),
3.57 (3H,s), 3.55-3.70 (1H,m), 4.20-4.30 (1H,m), 4.30-
15 4.40 (1H,m), 7.02 (1H,s), 7.17 (1H,dd, $J=8.5, 2.0\text{Hz}$),
7.41 (1H,d, $J=8.5\text{Hz}$), 7.71 (1H,s), 8.20-8.35 (1H,m), 8.35-
8.45 (1H,m), 11.82 (1H,br).

MS (FAB) m/z : 530 ($M+H$) $^+$.

[Example 52]

20 Ethyl (1R*,3S*,4R*)-3-{[(5-chloroindol-2-yl)carbonyl]-
amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:



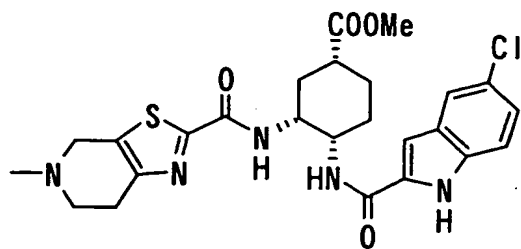
The title compound was obtained by treating the compound obtained in Referential Example 98 with a saturated ethanol solution of hydrochloric acid and then
 5 condensing it with 5-chloroindole-2-carboxylic acid in a similar manner to Example 49.

¹H-NMR (CDCl₃) δ: 1.29(3H,t,J=7.1Hz), 1.82-2.30(6H,m),
 2.49(3H,s), 2.62-2.73(1H,m), 3.74-3.85(2H,m), 3.85-
 3.93(2H,m), 3.71(2H,s), 4.12-4.29(3H,m), 4.49-4.59(1H,m),
 10 6.89(1H,br.s), 7.21(1H,dd,J=8.8, 2.0Hz),
 7.32(1H,d,J=8.8Hz), 7.33(1H,br.s), 7.41(1H,br.s),
 7.62(1H,br.s), 9.37(1H,s).

MS (ESI) m/z: 544 (M+H)⁺.

[Example 53]

15 Methyl (1R*,3R*,4S*)-4-([(5-chloroindol-2-yl)carbonyl]-
 amino)-3-([(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
 pyridin-2-yl)carbonyl]amino)cyclohexanecarboxylate:



The title compound was obtained by treating the

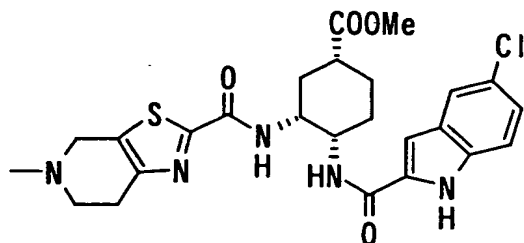
compound obtained in Referential Example 106 with a 4N dioxane solution of hydrochloric acid and then condensing it with 5-chloroindole-2-carboxylic acid in a similar manner to Example 49.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.65-1.80 (3H,m), 1.80-2.10 (2H,m), 2.15-2.25 (1H,m), 2.55-2.70 (1H,m), 2.89 (3H,s), 3.05-3.20 (1H,m), 3.30-3.50 (4H,m), 3.55-3.65 (1H,m), 3.62 (3H,s), 4.20-4.30 (1H,m), 4.35-4.45 (1H,m), 7.19 (1H,dd, $J=8.8, 1.2\text{Hz}$), 7.23 (1H,s), 7.43 (1H,d, $J=8.8\text{Hz}$), 7.73 (1H,s),
10 8.03 (1H,d, $J=6.8\text{Hz}$), 8.73 (1H,d, $J=8.5\text{Hz}$), 11.15-11.38 (1H,br), 11.85 (1H,s).

MS (FAB) m/z : 530 ($\text{M}+\text{H}$) $^+$.

[Example 54]

Methyl (1R,3R,4S)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-
15 3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:



The title compound was obtained by treating the compound obtained in Referential Example 112 a 4N dioxane
20 solution of hydrochloric acid and then condensing it with 5-chloroindole-2-carboxylic acid in a similar manner to Example 49.

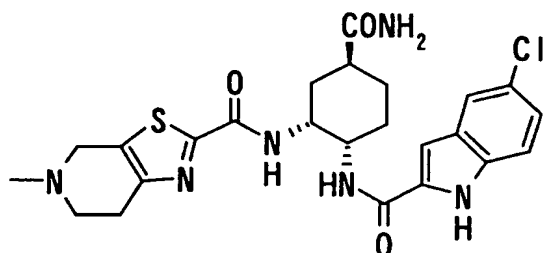
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.67-1.76 (3H,m), 1.88-1.91 (1H,m),

2.01 (1H, br. s), 2.13-2.22 (1H, m), 2.52-2.67 (4H, m),
2.86 (2H, br. s), 3.04 (2H, br. s), 3.33-3.41 (1H, m), 3.61 (3H, s),
4.22-4.36 (3H, m), 7.17-7.22 (2H, m), 7.42 (1H, d, J=8.8 Hz),
7.72 (1H, s), 8.00 (1H, d, J=6.9 Hz), 8.68 (1H, d, J=8.6 Hz),
5 11.80 (1H, s).

MS (FAB) m/z: 530 (M+H)⁺.

[Example 55]

N-((1R*, 2S*, 5S*)-5-(Aminocarbonyl)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-
10 tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



The title compound was obtained by treating the
compound obtained in Referential Example 113 with a 4N
dioxane solution of hydrochloric acid and then condensing
15 it with the compound obtained in Referential Example 10.

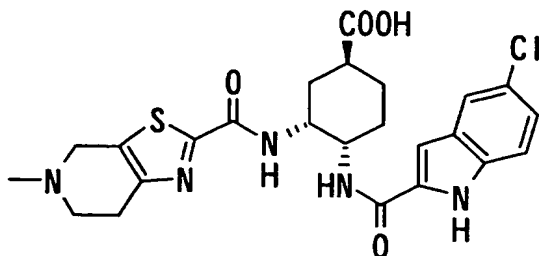
¹H-NMR (CDCl₃) δ: 0.78-2.40 (7H, m), 2.53 (3H, s), 2.80-
2.89 (1H, m), 2.91-3.00 (1H, m), 3.68-3.76 (2H, m), 4.08-
4.19 (1H, m), 4.54-4.65 (1H, m), 6.80 (1H, br. s),
7.21 (1H, dd, J=8.4, 1.6 Hz), 7.33 (1H, d, J=8.4 Hz), 7.38-
20 7.43 (1H, m), 7.49-7.55 (1H, m), 7.63 (1H, br. s), 9.14 (1H, br. s).

MS (ESI) m/z: 515 (M+H)⁺.

[Example 56]

(1R*, 3S*, 4R*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-3-

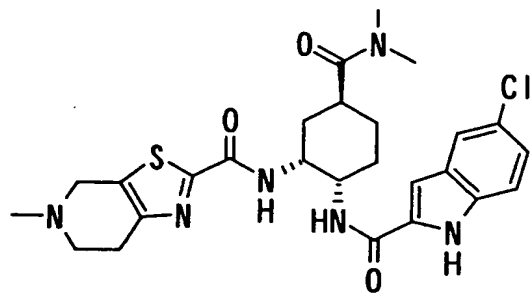
{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylic acid:



The compound (916 mg) obtained in Example 49 was
 5 suspended in a mixed solvent of ethanol (10 ml) and
 tetrahydrofuran (8 ml), and a 1N aqueous solution (3.3 ml)
 of sodium hydroxide was added at room temperature to stir
 the mixture for 12 hours at the same temperature. After
 adding 1N hydrochloric acid (3.3 ml), the solvent was
 10 distilled off under reduced pressure, and the residue was
 washed with water and diethyl ether to obtain the title
 compound (712 mg).

[Example 57]

N-{(1R*,2S*,5S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-
 15 5-[(dimethylamino)carbonyl]cyclohexyl)-5-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
 hydrochloride:



Triethylamine (0.25 ml), dimethylamine hydrochloride

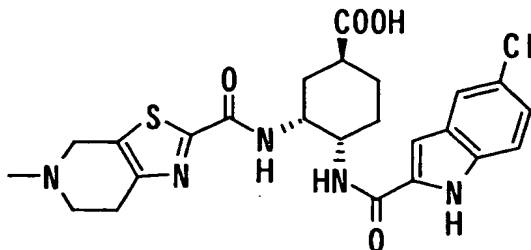
(133 mg), 1-hydroxybenzotriazole monohydrate (53 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (75 mg) were added to a chloroform suspension (10 ml) of the compound (168 mg) obtained in Example 56, and the mixture was stirred for 72 hours. The solvent was distilled off under reduced pressure, and water was added to the residue to conduct extraction with chloroform. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride: methanol = 93:7). The thus-obtained colorless solids (135 mg) were suspended in ethanol (5 ml), to which 1N ethanol solution (0.5 ml) of hydrochloric acid was added. The mixture was stirred for 2 hours, and the solvent was distilled off to obtain the title compound (112 mg).

¹H-NMR (DMSO-d₆) δ: 1.42-2.07 (6H,m), 2.73-3.70 (10H,m), 2.88 (3H,s), 2.97 (3H,s), 4.03-4.20 (1H,m), 4.51-4.67 (1H,m), 7.04 (1H,br.s), 7.16 (1H,br,J=8.8Hz), 7.41 (1H,d,J=8.8Hz), 7.68 (1H,br.s), 8.32-8.47 (2H,m), 10.76 (1H,br.s).

MS (ESI) m/z: 543 (M+H)⁺.

[Example 58]

(1S,3R,4S)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylic acid:



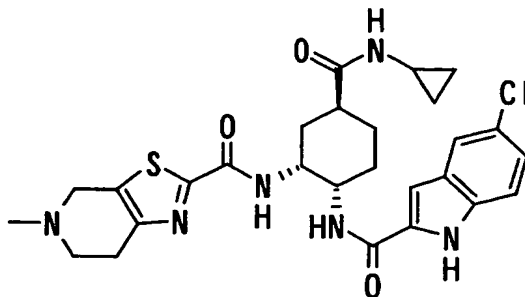
The compound (1.6 g) obtained in Example 50 was suspended in a mixed solvent of ethanol (20 ml) and tetrahydrofuran (15 ml), and a 1N aqueous solution (5.9 ml) of sodium hydroxide was added at room temperature to stir the mixture for 12 hours at the same temperature. After adding 1N hydrochloric acid (5.9 ml), the solvent was distilled off under reduced pressure, and the residue was washed with water and diethyl ether to obtain the title compound (1.19 g).

m.p. 234-236°C.

$[\alpha]_D -57^\circ$ (C=1.0, methanol).

[Example 59]

N-{(1R,2S,5S)-2-[[(5-Chloroindol-2-yl) carbonyl] amino]-5-[(cyclopropylamino) carbonyl] cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



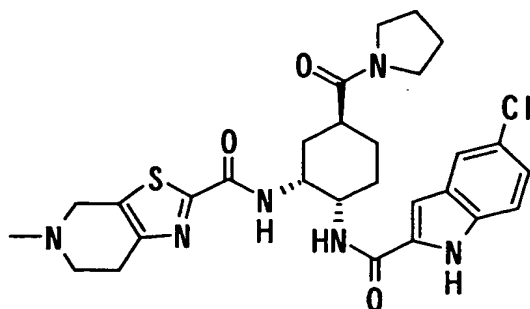
The title compound was obtained from the compound obtained in Example 58 and cyclopropylamine in a similar manner to Example 57.

¹H-NMR (DMSO-d₆) δ: 0.32-0.40 (2H,m), 0.53-0.63 (2H,m), 1.50-2.10 (6H,m), 2.25-2.40 (1H,m), 2.45-2.70 (2H,m), 2.91 (3H,s),
5 3.05-3.80 (3H,m), 4.05-4.17 (1H,m), 4.30-4.55 (2H,m), 4.55-4.80 (1H,m), 7.03 (1H,d,J=1.5Hz), 7.16 (1H,dd,J=8.8,2.0Hz), 7.41 (1H,d,J=8.8Hz), 7.68 (1H,d,J=2.0Hz), 7.86 (1H,br,J=3.4Hz), 8.06 (1H,br.s), 8.40 (1H,br,J=7.6Hz),
10 11.20-11.60 (1H,br), 11.79 (1H,s).

MS (FAB) m/z: 555 (M+H)⁺.

[Example 60]

N-[(1R,2S,5S)-2-[[(5-Chloroindol-2-yl)carbonyl]amino]-5-(pyrrolidin-1-ylcarbonyl)cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
15 hydrochloride:



The title compound was obtained from the compound obtained in Example 58 and pyrrolidine in a similar manner
20 to Example 57.

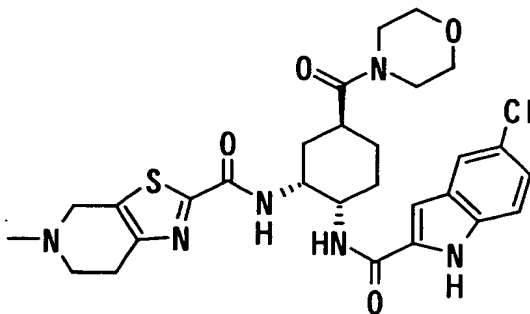
¹H-NMR (DMSO-d₆) δ: 1.45-2.10 (10H,m), 2.75-2.90 (2H,m), 2.90 (3H,s), 3.10-3.70 (H,m), 4.05-4.20 (1H,m), 4.25-

4.80 (3H, m), 7.05 (1H, s), 7.17 (1H, d, J=8.7 Hz),
7.41 (1H, d, J=8.7 Hz), 7.69 (1H, s), 8.32 (1H, br, J=7.6 Hz),
8.38 (1H, br, J=7.1 Hz), 11.22 (1H, br. s), 11.78 (1H, s).

MS (FAB) m/z: 569 (M+H)⁺.

5 [Example 61]

N-[(1R*,2S*,5S*)-2-[[(5-Chloroindol-2-yl) carbonyl] amino]-
5-(4-morpholinylcarbonyl) cyclohexyl]-5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
hydrochloride:



10

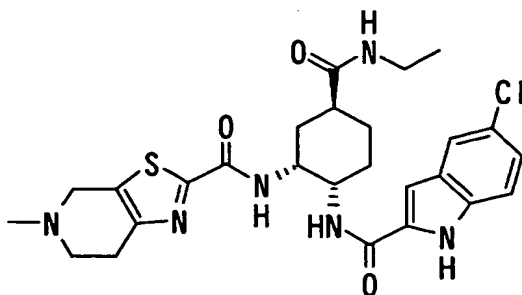
The title compound was obtained from the compound
obtained in Example 56 and morpholine in a similar manner
to Example 57.

¹H-NMR (DMSO-d₆) δ: 1.40-2.05 (6H, m), 2.75-3.70 (18H, m),
15 4.02-4.17 (1H, m), 4.55-4.69 (1H, m), 7.05 (1H, br. s),
7.17 (1H, br, J=8.8 Hz), 7.41 (1H, d, J=8.8 Hz), 7.67 (1H, br. s),
8.35 (1H, d, J=7.6 Hz), 8.40 (1H, d, J=7.6 Hz), 10.79 (1H, br. s).
MS (ESI) m/z: 585 (M+H)⁺.

[Example 62]

20 N-[(1R,2S,5S)-2-[[(5-Chloroindol-2-yl) carbonyl] amino]-5-
[(ethylamino) carbonyl] cyclohexyl]-5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide

hydrochloride:



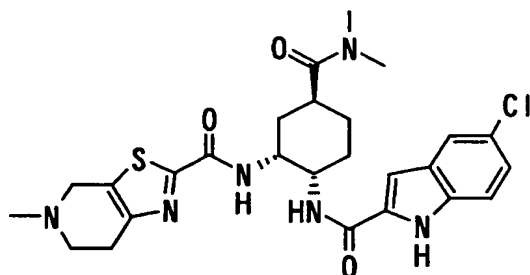
The compound (150 mg) obtained in Example 58 was dissolved in N,N-dimethylformamide (3 ml), to which N-ethylamine hydrochloride (119 mg), 1-hydroxybenzotriazole monohydrate (79 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (112 mg) and triethylamine (326 μ l) were added, and the mixture was stirred at room temperature for 4 days. The solvent was distilled off under reduced pressure, and a saturated aqueous solution of sodium hydrogencarbonate was added to the residue to conduct extraction with methylene chloride. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride: methanol = 47:3). The thus-obtained solid was dissolved in methylene chloride, to which 1N ethanol solution (171 μ l) of hydrochloric acid was added. The solvent was distilled off under reduced pressure, and methanol and diethyl ether were added to the residue to collect precipitate formed by filtration, thereby obtaining the title compound (74 mg).

¹H-NMR (DMSO-d₆) δ: 0.99 (3H, t, J=7.2Hz), 1.57-2.02 (6H, m), 2.33-2.38 (1H, m), 2.92 (3H, s), 3.01-3.08 (2H, m), 3.17-3.20 (2H, s), 3.45-3.70 (2H, m), 4.10-4.17 (1H, m), 4.40-4.69 (3H, m), 7.04 (1H, d, J=2.0Hz), 7.17 (1H, dd, J=8.8, 2.0Hz), 7.41 (1H, d, J=8.8Hz), 7.69 (1H, d, J=2.0Hz), 7.78-7.81 (1H, m), 8.08-8.12 (1H, m), 8.40 (1H, d, J=8.1Hz), 11.23 (1H, br. s), 11.79 (1H, br. s).

MS (FAB) m/z: 543 (M+H)⁺.

[Example 63]

10 N-((1R,2S,5S)-2-([(5-Chloroindol-2-yl) carbonyl] amino)-5-[(dimethylamino) carbonyl] cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



15 The compound (900 mg) obtained in Example 58 was dissolved in N,N-dimethylformamide (50 ml), to which dimethylamine hydrochloride (304 mg), 1-hydroxybenzotriazole monohydrate (262 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
20 (369 mg) and diisopropylethylamine (1.83 ml) were added, and the mixture was stirred at room temperature for 12 hours. The solvent was distilled off under reduced

pressure, and a saturated aqueous solution of sodium hydrogencarbonate was added to the residue to conduct extraction with methylene chloride. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent
5 was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride: methanol = 47:3). The thus-obtained white solids were dissolved in methylene chloride, to which 1N ethanol solution (1.49 ml) of
10 hydrochloric acid was added. The solvent was distilled off under reduced pressure, and methanol and diethyl ether were added to the residue to collect precipitate formed by filtration, thereby obtaining the title compound (777 mg).

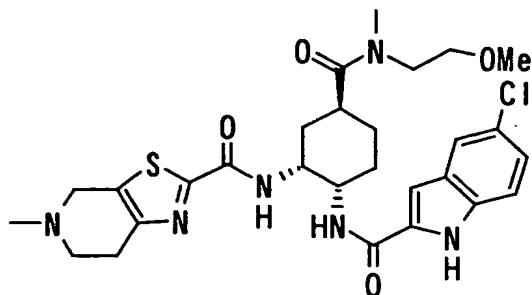
$[\alpha]_D = -53.9^\circ$ (18°C, c = 0.505, methanol).

15 $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.45-1.60 (1H,m), 1.70-1.85 (3H,m), 1.90-2.05 (2H,m), 2.80 (3H,s), 2.91 (3H,s), 2.95-3.10 (1H,m), 2.97 (3H,s), 3.10-3.75 (4H,m), 4.05-4.15 (1H,m), 4.35-4.75 (3H,m), 7.05 (1H,s), 7.16 (1H,dd, J=8.7, 2.1Hz), 7.41 (1H,d, J=8.6Hz), 7.67 (1H,s), 8.30-8.45 (2H,m),
20 11.63 (1H,br), 11.78 (1H,s).

MS (FAB) m/z: 543 (M+H) $^+$.

[Example 64]

N-((1R,2S,5S)-2-{{{(5-Chloroindol-2-yl)carbonyl}amino}-5-
{{(2-methoxyethyl)(methyl)amino}carbonyl}cyclohexyl)-5-
25 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-
carboxamide hydrochloride:



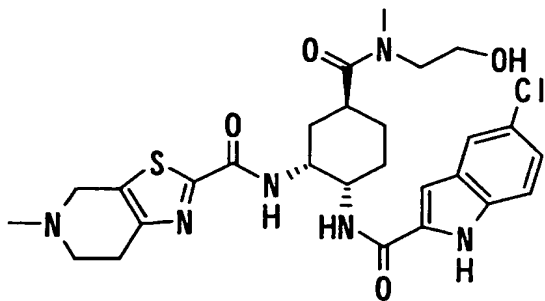
The title compound was obtained from the compound obtained in Example 58 in a similar manner to Example 57.

¹H-NMR (DMSO-d₆) δ: 1.50-1.99(6H,m), 2.80,3.01(3H,each s),
 5 2.91(3H,s), 3.03(1H,br.s), 3.16(2H,s), 3.23(3H,s), 3.35-
 3.67(6H,m), 4.09-4.16(1H,m), 4.43-4.67(3H,m), 7.04-
 7.06(1H,m), 7.16(1H,dd,J=8.8,2.0Hz), 7.42(1H,d,J=8.8Hz),
 7.69(1H,br.s), 8.29-8.41(2H,m), 11.59(1H,br.s),
 11.80(1H,br.s).

10 MS (FAB) m/z: 587(M+H)⁺.

[Example 65]

N-((1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-
 {[(2-hydroxyethyl)(methyl)amino]carbonyl}cyclohexyl)-5-
 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-
 15 carboxamide hydrochloride:



The title compound was obtained from the compound

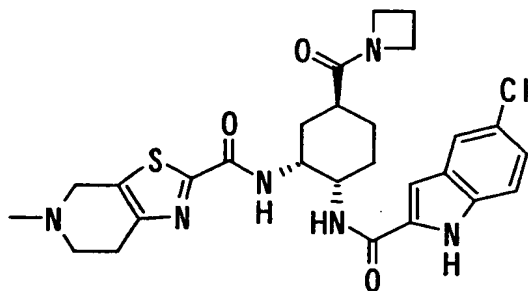
obtained in Example 58 in a similar manner to Example 57.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.50-1.55 (1H,m), 1.74-1.84 (3H,m), 1.94-1.97 (2H,m), 2.67, 3.02 (3H, each s), 2.91 (3H,s), 3.10-3.68 (9H,m), 4.11-4.13 (1H,m), 4.43-4.66 (4H,m), 7.05 (1H,s),
5 7.16 (1H,dd, $J=8.7, 2.0\text{Hz}$), 7.41 (1H,d, $J=8.7\text{Hz}$), 7.68 (1H,s),
8.34-8.40 (2H,m), 11.47 (1H,br.s), 11.79 (1H,s).

MS (FAB) m/z : 573 ($\text{M}+\text{H}$) $^+$.

[Example 66]

N-((1R,2S,5S)-5-(1-Azetidinylcarbonyl)-2-[[(5-chloroindol-
10 2-yl) carbonyl]amino]cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
hydrochloride:



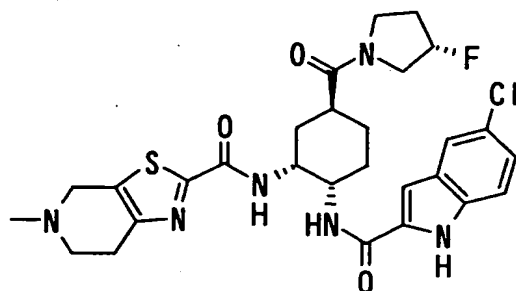
The title compound was obtained from the compound
15 obtained in Example 58 and azetidine hydrochloride in a
similar manner to Example 57.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.47-1.55 (1H,m), 1.65-1.82 (3H,m), 1.88-2.01 (2H,m), 2.16 (2H,quint., $J=7.6\text{Hz}$), 3.17-3.67 (5H,m),
3.82 (2H,t, $J=7.6\text{Hz}$), 4.02-4.14 (3H,m), 4.43-4.67 (3H,m),
20 7.06 (1H,s), 7.17 (1H,dd, $J=8.7, 1.7\text{Hz}$), 7.41 (1H,d, $J=8.7\text{Hz}$),
7.69 (1H,br.s), 8.31 (1H,d, $J=7.6\text{Hz}$), 8.38 (1H,d, $J=7.6\text{Hz}$),
11.41 (1H,br.s), 11.80 (1H,s).

MS (FAB) m/z : 555 ($M+H$)⁺.

[Example 67]

N-((1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-
{[(3S)-3-fluoropyrrolidinyl]carbonyl}cyclohexyl)-5-methyl-
5 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridinecarboxamide
hydrochloride:



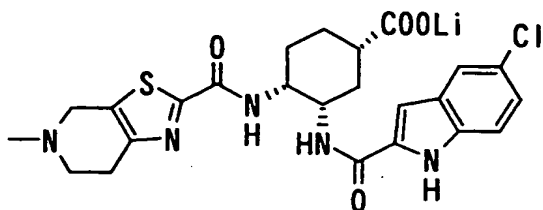
The title compound was obtained from the compound
obtained in Example 58 and (S)-3-fluoropyrrolidine
10 (Synlett., 1995, p. 55) in a similar manner to Example 57.

¹H-NMR (DMSO-d₆) δ : 1.23-3.77 (22H, m), 4.11-4.16 (1H, m),
4.58-4.51 (1H, m), 5.23-5.42 (1H, m), 7.05 (1H, s),
7.16 (1H, d, J=8.3 Hz), 7.42 (1H, d, J=8.3 Hz), 7.68 (1H, s), 8.34-
8.37 (2H, m), 11.78 (1H, s).

15 MS (FAB) m/z : 587 ($M+H$)⁺.

[Example 68]

Lithium (1R*,3R*,4S*)-3-{[(5-Chloroindol-2-yl)carbonyl]-
amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:

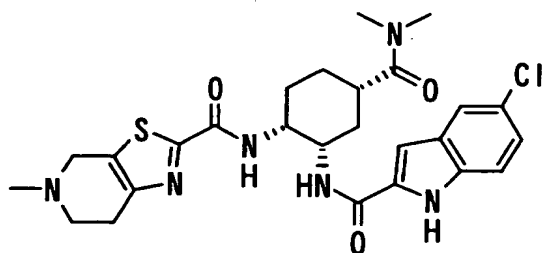


The compound (1.20 g) obtained in Example 51 was dissolved in tetrahydrofuran (32 ml), and lithium hydroxide (60.8 mg) and water (4 ml) were successively added under ice cooling to stir the mixture at room temperature for 14 hours. The solvent was distilled off under reduced pressure to obtain the title compound (1.12 g).

¹H-NMR (DMSO-d₆) δ: 1.55-1.70 (2H,m), 1.70-2.05 (4H,m), 2.10-2.20 (1H,m), 2.25-2.40 (4H,m), 2.50-2.80 (4H,m), 3.45-3.65 (3H,m), 4.10-4.30 (2H,m), 7.00-7.20 (2H,m), 7.50-7.65 (2H,m).

[Example 69]

N-{(1R*,2S*,4S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound

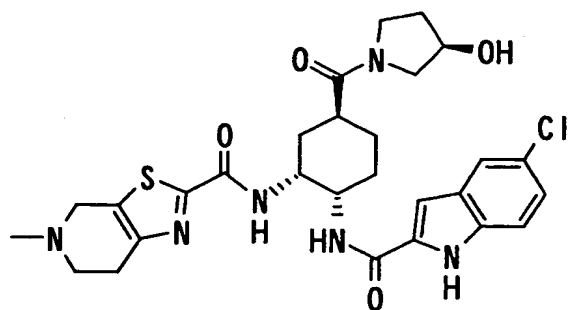
obtained in Example 68 and dimethylamine in a similar manner to Example 57.

¹H-NMR (DMSO-d₆) δ: 1.40-1.60 (2H,m), 1.65-1.80 (2H,m), 1.95-2.10 (2H,m), 2.84 (3H,s), 2.90-3.05 (1H,m), 2.92 (3H,s), 3.06 (3H,s), 3.15-3.75 (4H,m), 4.25-4.75 (4H,m), 7.02 (1H,d,J=1.5Hz), 7.15 (1H,dd,J=8.8,2.1Hz), 7.41 (1H,d,J=8.8Hz), 7.69 (1H,d,J=2.1Hz), 8.05 (1H,d,J=7.7Hz), 8.63 (1H,d,J=7.7Hz), 11.20 (1H,br), 11.79 (1H,s).

MS (FAB) m/z: 543 (M+H)⁺.

[Example 70]

N-((1R,2S,5S)-2-[[(5-Chloroindol-2-yl) carbonyl] amino]-5-[[(3R)-3-hydroxypyrrolidinyl] carbonyl] cyclohexyl-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



15

1) The compound (1.18 g) obtained in Referential Example 58 was dissolved in methanol (12 ml), 1N hydrochloric acid (240 μl) and palladium hydroxide (221 mg) were added, and hydrogen was introduced to conduct catalytic reduction under normal pressure at room temperature for 4.5 hours. The catalyst was removed by filtration, and the filtrate was concentrated to solid

under reduced pressure to obtain crude (3R)-3-[[tert-butyl(diphenyl)silyl]oxy]pyrrolidine hydrochloride (984 mg).

The thus-obtained product (249 mg), the product (295 mg) obtained in Example 58, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (126 mg) and 1-hydroxybenzotriazole monohydrate (87 mg) were dissolved in N,N-dimethylformamide (10 ml). Diisopropylethylamine (450 μ l) was added dropwise to the solution under ice cooling, and the mixture was stirred at room temperature for 12 hours. The solvent was distilled off under reduced pressure, methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was subjected to column chromatography on silica gel (methanol:methylene chloride = 3:97) to obtain N-((1R,2S,5S)-5-[[((3R)-3-[[tert-butyl(diphenyl)silyl]oxy]pyrrolidinyl)carbonyl]-2-[[[(5-chloroindol-2-yl)carbonyl]-amino)cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide (248 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.06(9H,s), 1.50-1.60(1H,m), 1.75-2.10(5H,m), 2.20-2.50(2H,m), 2.54(3H,d,J=2.8Hz), 2.60-3.00(5H,m), 3.30-3.80(6H,m), 4.10-4.20(1H,m), 4.40-4.70(2H,m), 6.85(1H,s), 7.15-7.25(1H,m), 7.30-7.50(8H,m), 7.60-7.70(5H,m), 7.90-8.00(1H,m), 9.38(1H,s).

MS (FAB) m/z: 823(M+H)⁺.

2) The above product (240 mg) was dissolved in pyridine (10 ml), and hydrogen fluoride-pyridine complex (3.0 ml) was added dropwise under ice cooling to stir the mixture at 0°C for 4.5 hours. Ethyl acetate (80 ml) was added to the reaction mixture under ice cooling to dilute it. The diluted reaction mixture was poured into ice. After sodium hydrogencarbonate was added to this solution to alkalify it, liquid separation was conducted. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride =1:19 → 1:9). The resultant crude purified product was dissolved in methylene chloride and methanol, to which 1N ethanol solution (225 µl) of hydrochloric acid was added to dry it once. Methanol and diethyl ether were added to the residue to solidify it, thereby obtaining the title compound (114 mg).

¹H-NMR (DMSO-d₆) δ: 1.50-1.60(1H,m), 1.70-2.10(6H,m), 2.75-2.85(1H,m), 2.92(3H,s), 3.10-3.80(8H,m), 4.10-5.10(6H,m), 7.05(1H,d,J=1.7Hz), 7.16(1H,dd,J=8.8,1.7Hz), 7.42(1H,d,J=8.8Hz), 7.68(1H,s), 8.30-8.45(2H,m), 11.10-11.40(1H,m), 11.78(1H,s).

MS (FAB) m/z: 585(M+H)⁺.

[Example 71]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5,5-

dimethoxycyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-
[5,4-c]pyridine-2-carboxamide or N-((1R*,2S*)-2-[[5-
chloroindol-2-yl)carbonyl]amino)-4,4-dimethoxycyclohexyl)-
5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-
5 carboxamide:

The title compound was obtained from the compound
obtained in Referential Example 118 and the compound
obtained in Referential Example 10 in a similar manner to
Example 2.

10 ¹H-NMR (CDCl₃) δ: 2.11-2.15(1H,m), 2.21-2.25(1H,m), 2.41-
2.43(1H,m), 2.46(3H,s), 2.70-2.75(1H,m), 2.81-
2.88(1H,m), 3.21(3H,s), 3.24(3H,s), 3.49(1H,s),
3.58(1H,d,J=15.6Hz), 3.71(1H,d,J=15.6Hz), 3.87-3.93(1H,m),
4.26-4.29(1H,m), 6.85(1H,d,J=2.0Hz),
15 7.19(1H,dd,J=8.5,2.0Hz), 7.30(1H,d,J=8.5Hz), 7.62(1H,s),
9.21(1H,s).

[Example 72]

N-((1R*,2S*)-2-[[5-Chloroindol-2-yl)carbonyl]amino)-5-
oxocyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
20 pyridine-2-carboxamide or N-((1R*,2S*)-2-[[5-chloroindol-
2-yl)carbonyl]amino)-4-oxocyclohexyl)-5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:

The compound (100 mg) obtained in Example 71 was
dissolved in chloroform (2 ml), and trifluoroacetic acid
25 (0.5 ml) and water (0.5 ml) were added to stir the mixture
at room temperature for 3.5 hours. A saturated aqueous
solution of sodium hydrogencarbonate was added to the

reaction mixture to conduct extraction with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:methanol = 19:1). The thus-obtained white solids were dissolved in methanol (4 ml), to which a 1N ethanol solution (0.38 ml) of hydrochloric acid was added. The solvent was distilled off under reduced pressure to obtain the title compound (35 mg).

¹H-NMR (DMSO-d₆) δ: 1.83-1.90(1H,m), 2.08-2.10(1H,m), 2.28-2.32(1H,m), 2.50-2.59(1H,m), 2.87(3H,s), 2.96(1H,t,J=13.0Hz), 3.06-3.10(2H,m), 3.33-3.36(3H,m), 4.02-4.04(2H,m), 4.55-4.57(2H,m), 7.03(1H,s), 7.15(1H,d,J=8.8Hz), 7.38(1H,d,J=8.8Hz), 7.69(1H,s), 8.43(1H,d,J=8.8Hz), 8.91(1H,d,J=8.8Hz), 11.75(1H,s).

[Example 73]

N-[(1R*,2S*)-2-{{[(5-Chloroindol-2-yl)carbonyl]amino}-5-(hydroxyimino)cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide or N-[(1R*,2S*)-2-{{[(5-chloroindol-2-yl)carbonyl]amino}-4-(hydroxyimino)-cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:

The compound (133 mg) obtained in Example 72 was dissolved in a mixed solvent of pyridine (8 ml) and methanol (8 ml), and hydroxylamine hydrochloride (30 mg)

was added to stir the mixture at room temperature for 3 days. The reaction mixture was concentrated, and water was added to the residue to conduct extraction with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 97:3 → 17:3) to obtain the title compound (131 mg).

¹H-NMR (CDCl₃) δ: 1.43-1.86(3H,m), 1.98-2.03(1H,m), 2.26-2.30(1H,m), 2.45(3H,s), 2.47-2.51(1H,m), 2.67-2.71(1H,m), 2.78-2.86(3H,m), 3.86-3.43(2H,m), 4.16-4.24(2H,m), 6.85(1H,s), 7.16-7.13(1H,m), 7.20-7.24(1H,m), 7.46,7.50(total 1H,s), 7.56-7.64(2H,m), 9.59,9.62(total 1H,s).

[Example 74]

N-((7R*,8S*)-8-[[(5-Chloroindol-2-yl)carbonyl]amino]-1,4-dioxaspiro[4.5]dec-7-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide or N-((7R*,8S*)-7-[[(5-chloroindol-2-yl)carbonyl]amino]-1,4-dioxaspiro[4.5]dec-8-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:

The title compound was obtained from the compound obtained in Referential Example 120 and the compound obtained in Referential Example 10 in a similar manner to Example 2.

¹H-NMR (CDCl₃) δ: 1.69-1.87 (6H,m), 2.14-2.17 (1H,m), 2.30-2.32 (1H,m), 2.47 (3H,s), 2.70-2.75 (1H,m), 2.81-2.89 (2H,m), 3.58 (1H,d,J=15.4Hz), 3.72 (1H,d,J=15.4Hz), 3.89-3.91 (1H,m), 3.99 (4H,s), 4.37-4.40 (1H,m), 6.86 (1H,d,J=2.0Hz), 7.19 (1H,dd,J=8.8,2.0Hz), 7.30 (1H,d,J=8.8Hz), 7.38 (1H,d,J=7.3Hz), 7.62 (1H,d,J=2.0Hz), 9.15 (1H,s).

[Example 75]

N-[(1R*,2S*)-2-{{(5-Chloroindol-2-yl)carbonyl}amino}-5-(methoxyimino)cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide or N-[(1R*,2S*)-2-{{(5-chloroindol-2-yl)carbonyl}amino}-4-(methoxyimino)-cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:

1) The compound (2.21 g) obtained in Referential Example 124 was dissolved in methylene chloride (30 ml), and trifluoroacetic acid (6 ml) was added to stir the mixture at room temperature for 1.5 hours. The reaction mixture was concentrated, dried with a vacuum pump and then dissolved in N,N-dimethylformamide (20 ml), to which 5-chloroindole-2-carboxylic acid (500 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (593 mg), 1-hydroxybenzotriazole monohydrate (473 mg) and N-methylmorpholine (2.8 ml) were added. The mixture was stirred at room temperature for 10 hours. Additionally, 5-chloroindole-2-carboxylic acid (242 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (237 mg) and 1-hydroxybenzotriazole monohydrate (189 mg)

were added to stir the mixture for 4 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct extraction with ethyl acetate and with a mixed solvent of ethyl acetate and tetrahydrofuran. The resultant organic layers were washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 97:3 → 4:1) to obtain N-[(1R*,2S*)-2-amino-5-(methoxyimino)cyclohexyl]-5-chloroindole-2-carboxamide (368 mg) and N-[(1R*,2S*)-2-amino-4-(methoxyimino)-cyclohexyl]-5-chloroindole-2-carboxamide (300 mg).

2) The title compound (mixture of syn and anti isomers at the methoxyimino group) from one of the above-obtained N-[(1R*,2S*)-2-amino-5-(methoxyimino)-cyclohexyl]-5-chloroindole-2-carboxamide or N-[(1R*,2S*)-2-amino-4-(methoxyimino)cyclohexyl]-5-chloroindole-2-carboxamide and the compound obtained in Referential Example 10 in a similar manner to Example 2.

¹H-NMR (CDCl₃) δ: 1.84-2.00 (3H,m), 2.26-2.56 (3H,m), 2.46 (3H,s), 2.80-2.83 (4H,m), 3.57 (1H,q,J=15.4Hz), 3.70 (1H,q,J=15.4Hz), 3.84,3.85 (total 3H,s), 4.08-4.14 (1H,m), 4.26-4.30 (1H,m), 6.84 (1H,s), 7.17 (1H,d,J=8.8Hz), 7.27 (1H,d,J=8.8Hz), 7.46-7.48 (2H,m), 7.56 (1H,m), 9.42,9.55 (total 1H,s).

[Example 76]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-hydroxycyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide (Stereoisomer A) or N-
5 ((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}-4-hydroxycyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide (Stereoisomer A):

1) N-((1R*,2S*)-2-amino-4-{[tert-butyl(diphenyl)silyl]oxy}cyclohexyl)-5-chloroindole-2-
10 carboxamide (Stereoisomer A) and N-((1R*,2S*)-2-amino-5-{[tert-butyl(diphenyl)silyl]oxy}cyclohexyl)-5-chloroindole-2-carboxamide (Stereoisomer A) were obtained by subjecting the ((1R*,2S*)-form obtained in Referential Example 125 to de(tert-butoxycarbonylation) in the same
15 manner as in the step 1) of Example 75 and reacting the formed product with 5-chloroindole-2-carboxylic acid.

2) N-((1R*,2S*)-5-{[tert-Butyl(diphenyl)silyl]oxy}-2-
{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
20 (Stereoisomer A) or N-((1R*,2S*)-4-{[tert-butyl(diphenyl)silyl]oxy}-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (Stereoisomer A) was obtained from the product obtained by
25 the above reaction and the compound obtained in Referential Example 10 in a similar manner to Example 2.

¹H-NMR (CDCl₃) δ: 1.06(9H,s), 1.55-1.61(1H,m), 1.85-

1.90 (1H,m), 2.18-2.25 (1H,m), 2.46 (3H,s),
2.51 (2H,d,J=7.6Hz), 2.72 (1H,m), 3.56 (1H,s),
3.57 (1H,d,J=15.3Hz), 3.72 (1H,d,J=15.3Hz), 3.71-3.81 (1H,m),
3.88-3.95 (1H,m), 6.78 (1H,s), 7.17 (1H,dd,J=2.0,8.8Hz),
5 7.37-7.44 (7H,m), 7.59 (1H,s), 7.65-7.68 (6H,m), 9.30 (1H,s).

3) The title compound was obtained from the compound obtained by the above-described reaction in the same manner as in the step 3) of Example 28.

¹H-NMR (DMSO-d₆) δ: 1.25-1.30 (2H,m), 1.45-1.64 (2H,m),
10 1.86 (1H,d,J=9.0Hz), 1.98-2.03 (1H,m), 2.66-2.73 (3H,s),
2.69 (2H,m), 2.75-2.79 (2H,m), 3.54 (1H,d,J=15.6Hz),
3.62 (1H,d,J=15.6Hz), 3.96-4.02 (2H,m), 4.78 (1H,d,J=4.2Hz),
7.00 (1H,s), 7.14 (1H,dd,J=2.0,8.8Hz), 7.38 (1H,d,J=8.8Hz),
7.66 (1H,s), 8.20 (1H,d,J=7.8Hz), 8.54 (1H,d,J=7.8Hz),
15 11.69 (1H,s).

[Example 77]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-hydroxy-5-methylcyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
20 (Stereoisomer A1) or N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}-4-hydroxy-4-methylcyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (Stereoisomer A2):

The title compounds were obtained by reacting the
25 compound obtained in Referential Example 128 with the compound obtained in Referential Example 10 in a similar manner to Example 2.

Stereoisomer A1:

¹H-NMR (DMSO-d₆) δ: 1.24 (3H, s), 1.33-1.82 (4H, m), 2.34 (3H, s),
2.67-3.64 (8H, m), 4.02-4.10 (2H, m), 4.67 (1H, br. s),
7.02 (1H, s), 7.13 (1H, d, J=8.6 Hz), 7.38 (1H, d, J=8.6 Hz),
7.66 (1H, d, J=2.0 Hz), 8.21-8.26 (1H, br), 8.59 (1H, d, J=8.1 Hz),
11.73 (1H, br. s)

MS (FAB) m/z: 502 (M+H)⁺.

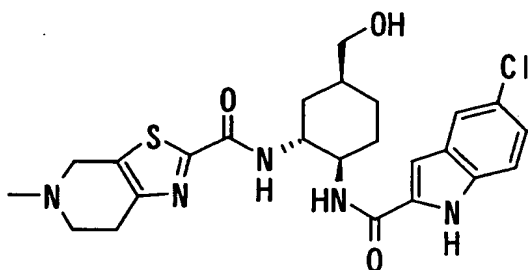
Stereoisomer A2:

¹H-NMR (DMSO-d₆) δ: 1.25 (3H, s), 1.33-1.79 (4H, m), 2.33 (3H, s),
2.65-3.63 (8H, m), 3.88-3.94 (1H, m), 4.20-4.25 (1H, m),
4.59 (1H, br), 7.01 (1H, s), 7.13 (1H, d, J=7.8 Hz),
7.38 (1H, d, J=8.6 Hz), 7.67 (1H, s), 8.29 (1H, br),
8.43 (1H, d, J=9.3 Hz), 11.67 (1H, br)

MS (FAB) m/z: 502 (M+H)⁺.

[Example 78]

N-[(1R*,2R*,5S*)-2-[[(5-Chloroindol-2-yl) carbonyl] amino]-
5-(hydroxymethyl) cyclohexyl]-5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



The title compound was obtained by treating the
compound obtained in Referential Example 129 with an
ethanol solution of hydrochloric acid and then condensing

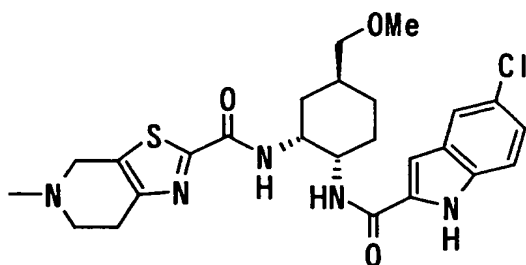
it with the compound obtained in Referential Example 10 in a similar manner to Example 49.

¹H-NMR (DMSO-d₆) δ: 1.42-1.90(5H,m), 2.07-2.26(3H,m), 2.46(3H,s), 2.67-2.95(4H,m), 3.55-3.80(4H,m), 3.80-3.95(1H,m), 4.13-4.25(1H,m), 6.84(1H,br.s), 7.17(1H,dd,J=8.8,2.0Hz), 7.23-7.35(2H,m), 7.43(1H,d,J=7.2Hz), 7.58(1H,br.s), 9.29(1H,s).

MS (ESI) m/z: 502 (M+H)⁺.

[Example 79]

10 N-[(1R*,2S*,5S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-(methoxymethyl)cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



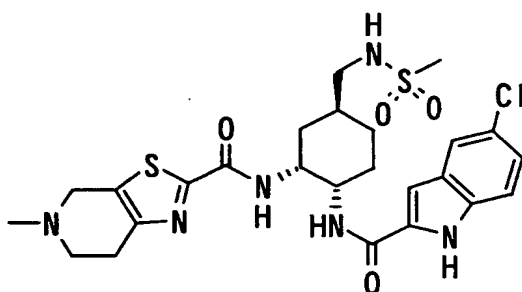
The title compound was obtained by treating the compound obtained in Referential Example 135 with an ethanol solution of hydrochloric acid and then condensing it with the compound obtained in Referential Example 10 in a similar manner to Example 49.

¹H-NMR (CDCl₃) δ: 1.20-1.38(1H,m), 1.50-1.67(2H,m), 1.88-2.03(2H,m), 2.03-2.14(1H,m), 2.21-2.32(1H,m), 2.53(3H,s), 2.75-2.95(2H,m), 3.20-3.35(2H,m), 3.37(3H,s), 3.73(1H,d,J=16.0Hz), 3.76(1H,d,J=16.0Hz), 4.04-4.13(1H,m), 4.53-

4.62 (1H,m), 6.85 (1H,d,J=2.0Hz), 7.19 (1H,dd,J=8.8,2.0Hz),
7.33 (1H,d,J=8.8Hz), 7.54 (1H,d,J=7.2Hz), 7.63 (1H,d,J=2.0Hz),
8.07 (1H,d,J=5.6Hz), 9.49 (1H,br.s).

[Example 80]

- 5 N-((1R*,2S*,5S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-
{[(methanesulfonyl)amino]methyl}cyclohexyl)-5-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



- 1) The compound (437 mg) obtained in Referential
10 Example 137 was dissolved in ethanol (5 ml), and a 4N
dioxane solution (5 ml) of hydrochloric acid was added at
room temperature to stir the mixture for 13 hours. The
solvent was distilled off, and the residue was dissolved
in N,N-dimethylformamide (10 ml) , to which triethylamine
15 (0.7 ml), the compound (300 mg) obtained in Referential
Example 10, 1-hydroxybenzotriazole monohydrate (162 mg)
and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride (230 mg) were added. The mixture was stirred
for 13 hours, and water was added to the reaction mixture
20 to conduct extraction with chloroform. The resultant
organic layer was washed with a saturated aqueous solution
of sodium hydrogencarbonate and saturated aqueous solution

of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride: methanol = 97:3) to obtain N- ((1R*,2S*,5S*)-5-(azidomethyl)-2-[[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (330 mg).

¹H-NMR (DMSO-d₆) δ: 1.15-2.08 (7H,m), 2.33 (3H,s), 2.34-2.95 (6H,m), 3.64 (2H,s), 4.05-4.17 (1H,m), 4.36-4.47 (1H,m), 7.02 (1H,s), 7.15 (1H,dd,J=8.8,2.0Hz), 7.40 (1H,d,J=8.8Hz), 7.67 (1H,d,J=2.0Hz), 8.02 (1H,d,J=7.6Hz), 8.44 (1H,d,J=7.6Hz), 11.8 (1H,s).

2) The compound (300 mg) obtained by the above reaction was dissolved in ethanol (8 ml), and a catalytic amount of 10% palladium on carbon was added to stir the mixture at room temperature for 168 hours in a hydrogen atmosphere. Insoluble matter was filtered, and the solvent was distilled off. The thus-obtained crude N- ((1R*,2S*,5S*)-5-(aminomethyl)-2-[[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (150 mg) was dissolved in chloroform (6 ml), and triethylamine (0.2 ml) and methanesulfonyl chloride (0.035 ml) were added to stir the mixture for 13 hours. The solvent was distilled off under reduced pressure, and water was added to the residue to conduct extraction with chloroform. The

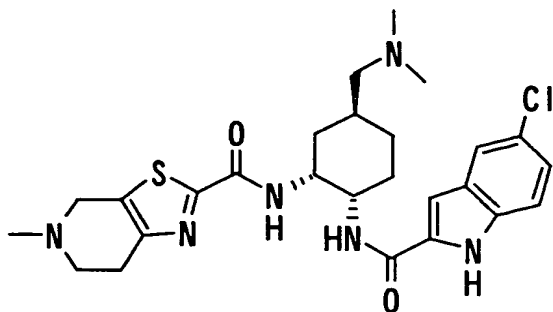
resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride: methanol = 24:1) to obtain the title compound (56 mg).

¹H-NMR (CDCl₃) δ: 1.18-1.34 (2H,m), 1.50-1.75 (4H,m), 1.90-2.30 (4H,m), 2.53 (3H,s), 2.78-2.90 (2H,m), 2.90-3.05 (6H,m), 3.20-3.30 (1H,m), 3.68-3.81 (2H,m), 3.98-4.08 (1H,m), 4.54-4.62 (1H,m), 6.10-6.19 (1H,m), 6.86 (1H,s), 7.19 (1H,dd,J=8.8,2.0Hz), 7.35 (1H,d,J=8.8Hz), 7.52 (1H,d,J=7.6Hz), 7.62 (1H,d,J=2.0Hz), 8.21 (1H,d,J=5.6Hz), 9.89 (1H,s).

MS (ESI) m/z: 579 (M+H)⁺.

[Example 81]

N-((1R*,2S*,5S*)-2-(((5-Chloroindol-2-yl)carbonyl)amino)-5-((dimethylamino)methyl)cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide trifluoroacetate:



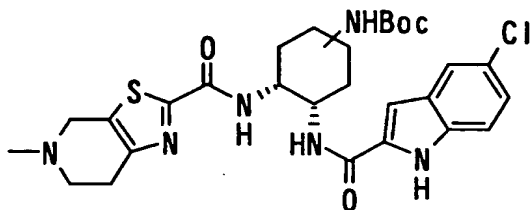
The title compound was obtained from the amine obtained in the step 2) of Example 80 in a similar manner to Example 24.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.15-2.22 (7H,m), 2.40-2.65 (2H,m), 2.68-2.85 (6H,m), 2.92-3.08 (5H,m), 3.10-3.18 (2H,m), 4.08-4.20 (1H,m), 4.35-4.51 (2H,m), 7.04 (1H,s), 7.14-7.20 (1H,m), 7.41 (1H,d, $J=8.8\text{Hz}$), 7.67 (1H,s), 8.25-8.42 (2H,m), 9.11 (1H,br.s), 9.89 (1H,s).

10 MS (ESI) m/z : 529 ($\text{M}+\text{H}$) $^+$.

[Example 82]

tert-Butyl (3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexylcarbamate (Isomer B)
 15 and tert-butyl (3R*,4S*)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexylcarbamate (Isomer B):



The compound (Stereoisomer B) (1.79 g) obtained in Referential Example 140 was dissolved in tetrahydrofuran (36 ml), and 10% palladium on carbon (0.40 g) was added to stir the mixture at room temperature for 20 hours in a hydrogen atmosphere. After the catalyst was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was dissolved in N,N-dimethylformamide (36 ml), to which p-nitrophenyl 5-chloroindole-2-carboxylate (2.02 g) was added to stir the mixture for 16 hours. The reaction mixture was concentrated under reduced pressure, and ethyl acetate and water were added to the residue to collect insoluble matter by filtration. The product was washed with ethyl acetate to obtain crude tert-butyl (3R*,4S*)-3-amino-4-[[(5-chloroindol-2-yl)carbonyl]amino]cyclohexylcarbamate (or (3R*,4S*)-4-amino-3-[[(5-chloroindol-2-yl)carbonyl]-amino]cyclohexylcarbamate) (Isomer B1) (1.49 g). The organic layer of the filtrate was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride: methanol = 30:1 → 10:1) to obtain tert-butyl

(3R*,4S*)-4-amino-3-[[(5-chloroindol-2-yl) carbonyl] amino]-cyclohexylcarbamate (or tert-butyl (3R*,4S*)-3-amino-4-[[(5-chloroindol-2-yl) carbonyl] amino] cyclohexylcarbamate) (Isomer B2) (0.37 g).

5 One of the title compounds was obtained from the Isomer B1 and the compound obtained in Referential Example 10 in a similar manner to Example 2.

¹H-NMR (DMSO-d₆) δ: 1.25-1.50 (1H,m), 1.37 (9H,s), 1.50-1.65 (1H,m), 1.75-2.20 (4H,m), 2.37 (3H,s), 2.70-3.00 (4H,m),
10 3.60-3.80 (3H,m), 4.13 (1H,br.a), 4.43 (1H,br.s),
6.92 (1H,d,J=7.1Hz), 7.05 (1H,s), 7.17 (1H,dd,J=8.8,2.2Hz),
7.41 (1H,d,J=8.8Hz), 7.69 (1H,s), 8.15 (1H,d,J=7.8Hz),
8.37 (1H,d,J=7.1Hz), 11.78 (1H,s).

MS (FAB) m/z: 587 (M+H)⁺.

15 The other title compound was obtained from the Isomer B2 in the same manner.

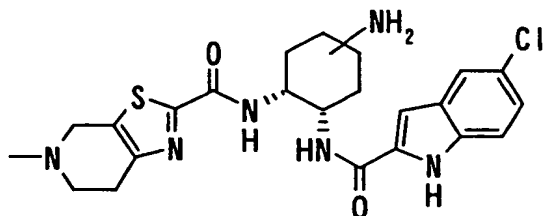
¹H-NMR (DMSO-d₆) δ: 1.15-1.30 (1H,m), 1.35 (9H,s), 1.45-1.60 (1H,m), 1.65-1.75 (1H,m), 1.85-1.95 (1H,m), 2.05-2.20 (2H,m), 2.34 (3H,s), 2.65-2.85 (4H,m), 3.55-3.70 (3H,m),
20 4.05-4.14 (1H,m), 4.40 (1H,br.s), 6.80 (1H,d,J=7.3Hz), 7.15-7.25 (2H,m), 7.43 (1H,d,J=8.8Hz), 7.73 (1H,d,J=2.0Hz),
8.05 (1H,d,J=6.6Hz), 8.51 (1H,d,J=8.8Hz), 11.82 (1H,s).

MS (FAB) m/z: 587 (M+H)⁺.

[Example 83]

25 N-((1R*,2S*)-5-Amino-2-[[(5-chloroindol-2-yl) carbonyl]-amino] cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide (or N-((1R*,2S*)-4-amino-2-

{[(5-chloroindol-2-yl)carbonyl]amino)cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide) hydrochloride (Stereoisomer B):



5 The compound (Stereoisomer B) (1.11 g) synthesized from Isomer B1 in Example 82 was suspended in methylene chloride (20 ml), and an ethanol solution (20 ml) of hydrochloric acid was added to stir the mixture at room temperature for 2 hours. The solvent was distilled off
10 under reduced pressure, and the residue was purified by gel filtration (Sephadex LH-20, methanol) to obtain the title compound (1.05 g).

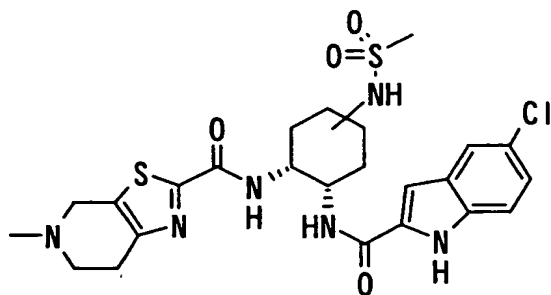
¹H-NMR (DMSO-d₆) δ: 1.55-1.65(1H,m), 1.75-1.90(2H,m), 1.95-2.20(2H,m), 2.20-2.40(1H,m), 2.90(3H,s), 3.10-3.20(1H,m),
15 3.20-3.50(3H,m), 3.65-3.75(1H,m), 4.10-4.20(1H,m), 4.35-4.50(1H,m), 4.55-4.65(1H,m), 4.65-4.75(1H,m), 7.07(1H,s), 7.17(1H,dd,J=8.8,2.0Hz), 7.42(1H,d,J=8.8Hz), 7.69(1H,s), 8.05-8.30(3H,br), 8.40-8.50(2H,m), 11.70-11.90(2H,m).

MS (FAB) m/z: 487(M+H)⁺.

20 [Example 84]

N-{(1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-[(methylsulfonyl)amino]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide or N-

{(1R*,2S*)-2-[[(5-Chloroindol-2-yl) carbonyl] amino]-4-
 [(methylsulfonyl) amino] cyclohexyl]-5-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
 (Stereoisomer B):



5

The compound (0.20 g) obtained in Example 83 was
 suspended in methylene chloride (7 ml), and triethylamine
 (0.16 ml) and methanesulfonyl chloride (28 μ l) were added
 to stir the mixture at room temperature for 20 hours.
 10 After the reaction mixture was diluted with methylene
 chloride, it was washed with an aqueous solution of sodium
 hydroxide and dried over anhydrous sodium sulfate. The
 solvent was distilled off under reduced pressure, and the
 residue was purified by column chromatography on silica
 15 gel (methylene chloride:methanol = 30:1 \rightarrow 15:1) to obtain
 the title compound (67.9 mg).

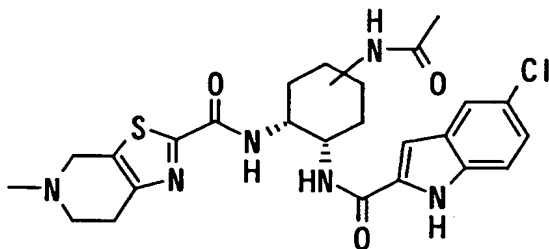
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.40-1.55(1H,m), 1.65-1.85(2H,m), 1.90-
 2.05(2H,m), 2.15-2.25(1H,m), 2.41(3H,s), 2.75-2.95(4H,m),
 2.92(3H,s), 3.55-3.80(3H,m), 4.10-4.20(1H,m), 4.45-
 20 4.55(1H,m), 7.08(1H,s), 7.15-7.20(2H,m),
 7.41(1H,d,J=8.8Hz), 7.69(1H,s), 8.27(1H,d,J=7.3Hz),
 8.33(1H,d,J=8.1Hz), 11.77(1H,s).

MS (FAB) m/z: 565 (M+H)⁺.

[Example 85]

N-((1R*,2S*)-5-(Acetylamino)-2-[[(5-chloroindol-2-yl)-
carbonyl]amino]cyclohexyl)-5-methyl-4,5,6,7-

5 tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide or N-
((1R*,2S*)-4-(acetylamino)-2-[[(5-chloroindol-2-yl)-
carbonyl]amino]cyclohexyl)-5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
(Stereoisomer B):



10

The compound (Stereoisomer B) (0.20 g) obtained in
Example 83 was suspended in methylene chloride (7 ml), and
triethylamine (0.16 ml) and acetic anhydride (34 μ l) were
added to stir the mixture at room temperature for 20 hours.

15 Methylene chloride and an aqueous solution of sodium
hydroxide were added to the reaction mixture to separate
insoluble matter by filtration. The organic layer of the
filtrate was separated and dried over anhydrous sodium
sulfate, and the solvent was then distilled off under
20 reduced pressure. The residue was purified by column
chromatography on silica gel (methylene chloride:methanol
= 15:1 \rightarrow 10:1) to obtain the title compound (0.12 g).

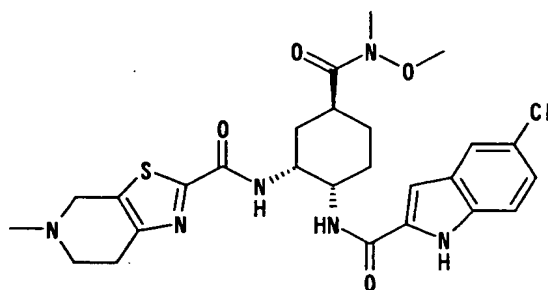
¹H-NMR (DMSO-d₆) δ : 1.35-1.50 (1H,m), 1.55-1.70 (1H,m),

1.80 (3H, s), 1.80-2.05 (3H, m), 2.05-2.20 (1H, m), 2.47 (3H, s),
 2.80-3.00 (4H, m), 3.75-4.00 (3H, m), 4.15-4.30 (1H, m), 4.45-
 4.55 (1H, m), 7.07 (1H, s), 7.17 (1H, dd, J=8.8, 1.0 Hz),
 7.41 (1H, d, J=8.8 Hz), 7.69 (1H, s), 7.89 (1H, d, J=7.3 Hz),
 8.24 (1H, d, J=8.1 Hz), 8.31 (1H, d, J=7.3 Hz), 11.77 (1H, s).

MS (FAB) m/z: 528 (M+H)⁺.

[Example 86]

N-((1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-
 {[methoxy(methyl)amino]carbonyl}cyclohexyl)-5-methyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
 hydrochloride:



The compound (250 mg) obtained in Example 58 was
 dissolved in N,N-dimethylformamide (5 ml), and N,O-
 dimethylhydroxylamine hydrochloride (142 mg), 1-(3-
 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
 (111 mg), 1-hydroxybenzotriazole monohydrate (89 mg) and
 N-methylmorpholine (213 ml) were added to stir the mixture
 at room temperature for 19 hours. After the reaction
 mixture was concentrated, an aqueous solution of sodium
 hydrogencarbonate was added to the residue to conduct
 extraction with ethyl acetate. After the resultant organic

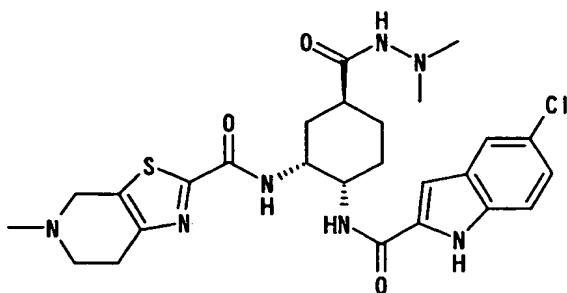
layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 47:3 → 23:2) to obtain a colorless amorphous solid (179 mg). This product was dissolved in methanol-tetrahydrofuran, and 1N ethanol solution (960 ml) of hydrochloric acid was added to obtain the title compound.

¹H-NMR (DMSO-d₆) δ: 1.57-1.91(4H,m), 1.96-2.00(1H,m), 2.10-2.21(1H,m), 2.92(3H,s), 2.93-3.03(2H,m), 3.08(3H,s), 3.10-3.28(2H,m), 4.16-4.19(1H,m), 4.50-4.52(1H,m), 4.69(1H,br.s), 7.06(1H,s), 7.17(1H,dd,J=8.8,1.5Hz), 7.42(1H,d,J=8.8Hz), 7.70(1H,s), 8.33(1H,br.s), 8.41(1H,d,J=7.8Hz), 11.81(1H,br.s).

MS (ESI) m/z: 559(M+H)⁺.

[Example 87]

N-{(1R,2S,5S)-2-[[(5-Chloroindol-2-yl)carbonyl]amino]-5-[(2,2-dimethylhydrazino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



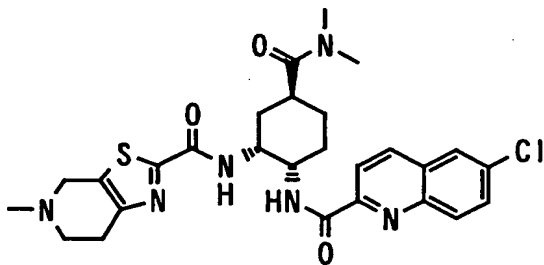
The title compound was obtained from the compound obtained in Example 58 and N,N-dimethylhydrazine in a similar manner to Example 57.

¹H-NMR (DMSO-d₆) δ: 1.49-1.54 (1H,m), 1.76-1.81 (2H,m), 1.89-1.93 (2H,m), 2.07-2.17 (1H,m), 2.33-3.60 (14H,m), 4.15-4.19 (1H,m), 4.40-4.47 (2H,m), 4.70-4.72 (1H,m), 7.04 (1H,s), 7.17 (1H,dd,J=8.5,2.0Hz), 7.42 (1H,d,J=8.5Hz), 7.70 (1H,s), 8.17-8.22 (1H,m), 8.41-8.43 (1H,m), 11.80 (1H,br.s).

MS (ESI) m/z: 558 (M+H)⁺.

10 [Example 88]

6-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino)cyclohexyl)-2-quinolinecarboxamide hydrochloride:



15

The title compound was obtained by treating the compound obtained in Referential Example 145 with an ethanol solution of hydrochloric acid in a similar manner to Example 49 and then condensing it with the compound obtained in Referential Example 10.

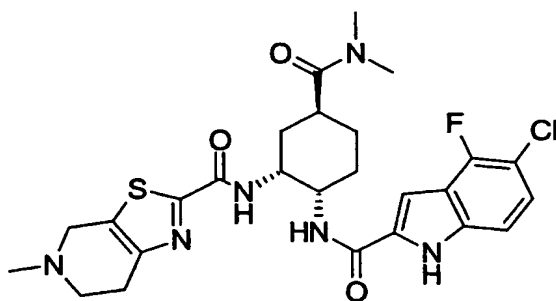
¹H-NMR (DMSO-d₆) δ: 1.45-1.60 (1H,m), 1.75-1.90 (3H,m), 1.90-2.00 (1H,m), 2.00-2.20 (1H,m), 2.80 (3H,s), 2.90 (3H,s),

2.99(3H,s), 3.10-3.30(5H,m), 3.56(1H,br), 4.10-4.20(1H,m),
4.40-4.70(2H,m), 7.88(2H,s), 8.15(1H,d,J=8.6Hz),
8.22(1H,s), 8.52(1H,d,J=8.6Hz), 8.72(1H,d,J=8.3Hz),
8.89(1H,d,J=8.3Hz).

5 MS (FAB) m/z: 555(M+H)⁺.

[Example 89]

N-((1R,2S,5S)-2-(((5-Chloro-4-fluoroindol-2-yl)carbonyl)-
amino)-5-((dimethylamino)carbonyl)cyclohexyl)-5-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
10 hydrochloride:



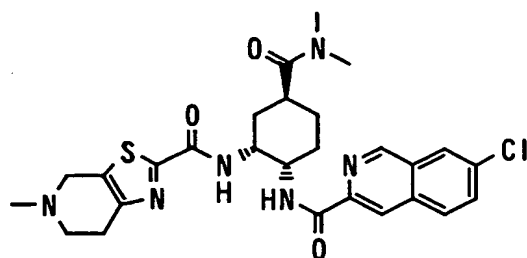
The title compound was obtained by condensing the
compound obtained in Referential Example 144 with the
compound obtained in Referential Example 274 in a similar
15 manner to Referential Example 91 and treating the
resultant compound with a 4N dioxane solution of
hydrochloric acid and then with the compound obtained in
Referential Example 10.

¹H-NMR (DMSO-d₆) δ:1.24-1.98(6H,m), 2.33-3.33(6H,m),
20 2.81(3H,s), 2.90(3H,s), 2.99(3H,s), 4.12(1H,br.s), 4.30-
4.70(1H,m), 4.60(1H,br.s), 7.21(1H,s), 7.27(2H,br.s),
8.37(1H,d,J=8.1Hz), 8.43(1H,d,J=7.6Hz), 12.11(1H,s).

MS (FAB) m/z : 561 (M+H)⁺.

[Example 90]

7-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-carbonyl]amino)cyclohexyl)isoquinoline-3-carboxamide hydrochloride:



The title compound was obtained by treating the compound obtained in Referential Example 146 with an ethanol solution of hydrochloric acid in a similar manner to Example 49 and then condensing it with the compound obtained in Referential Example 10.

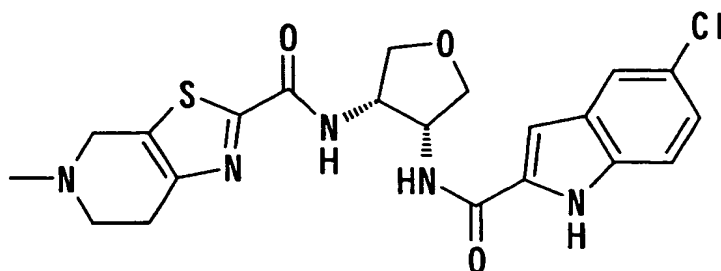
¹H-NMR (DMSO-*d*₆) δ : 1.45-1.65 (1H, m), 1.70-1.85 (3H, m), 1.95-2.10 (1H, m), 2.10-2.20 (1H, m), 2.80 (3H, s), 2.92 (3H, s), 2.96 (3H, s), 2.95-3.10 (1H, m), 3.10-3.40 (3H, m), 3.70-3.80 (1H, m), 4.20-4.30 (1H, m), 4.40-4.60 (2H, m), 4.65-4.80 (1H, m), 7.83-7.93 (1H, m), 8.26 (1H, d, $J=8.8$ Hz), 8.38 (1H, s), 8.60 (1H, s), 8.85-9.00 (2H, m), 9.30-9.40 (1H, m).

MS (FAB) m/z : 555 (M+H)⁺.

[Example 91]

N-((3R*,4S*)-4-[(5-Chloroindol-2-yl)carbonyl]amino)-tetrahydrofuran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo-

[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (0.1 g) obtained in Referential Example 10, 1-hydroxybenzotriazole monohydrate (78 mg) and 1-(3-
5 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.2 g) were successively added to a solution of the compound (0.12 g) obtained in Referential Example 172 in N,N-dimethylformamide (20 ml), and the mixture was stirred at room temperature for 1 day. After the reaction mixture
10 was concentrated, and the resultant residue was diluted with chloroform-methanol (9:1) and washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, the resultant organic layer was dried over anhydrous sodium sulfate, and the
15 solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform:methanol = 95:5) to obtain a free base of the title compound. This product was treated with an ethanol solution of hydrochloric acid to obtain the title
20 compound (0.1 g).

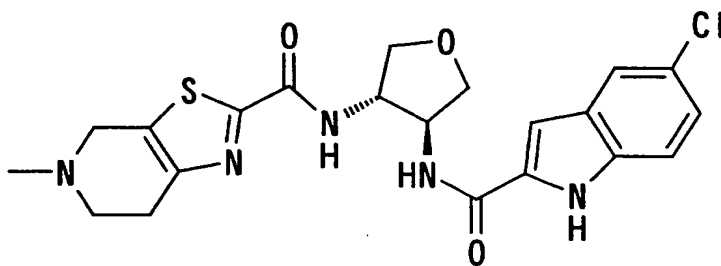
$^1\text{H-NMR}$ (CDCl_3) δ : 2.50 (3H, s), 2.70-2.90 (4H, m), 3.67 (1H, s), 3.70 (1H, s), 3.86 (1H, dd, $J=9.2, 6.3\text{Hz}$), 3.97 (1H, dd, $J=9.7, 4.1\text{Hz}$), 4.15 (1H, dd, $J=9.7, 5.8\text{Hz}$),

4.24 (1H, dd, J=9.2, 7.0Hz), 4.75-4.89 (1H, m), 4.92-5.03 (1H, m),
6.88 (1H, s), 7.20 (1H, dd, J=8.8, 2.0Hz), 7.33 (1H, d, J=8.8Hz),
7.35-7.43 (1H, m), 7.58 (1H, d, J=2.0Hz), 7.64 (1H, d, J=7.1Hz),
9.38 (1H, s).

5 MS (FAB) m/z: 460 (M+H⁺).

[Example 92]

N-((3S,4S)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-
tetrahydrofuran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo-
[5,4-c]pyridine-2-carboxamide:



10

The title compound was obtained from the compound
obtained in Referential Example 183 in accordance with the
processes of Referential Example 172 and Example 91.

¹H-NMR (CDCl₃) δ: 2.51 (3H, s), 2.83 (2H, t, J=5.3Hz),

15 2.93 (2H, t, J=5.3Hz), 3.72 (2H, s), 3.78-3.89 (2H, m),

4.31 (1H, dd, J=9.2, 7.3Hz), 4.41-4.56 (2H, m), 4.63-4.75 (1H, m),

6.88 (1H, s), 7.22 (1H, dd, J=8.8, 2.0Hz), 7.32 (1H, d, J=8.8Hz),

7.35-7.46 (1H, m), 7.55 (1H, d, J=7.1Hz), 7.60 (1H, d, J=2.0Hz),

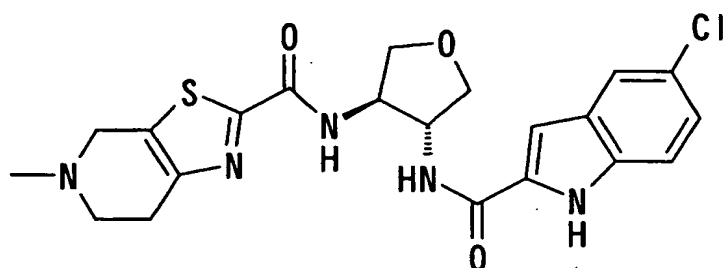
9.38 (1H, s).

20 MS (FAB) m/z: 460 (M+H⁺).

[Example 93]

N-((3R,4R)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-
tetrahydrofuran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo-

[5,4-c]pyridine-2-carboxamide hydrochloride:

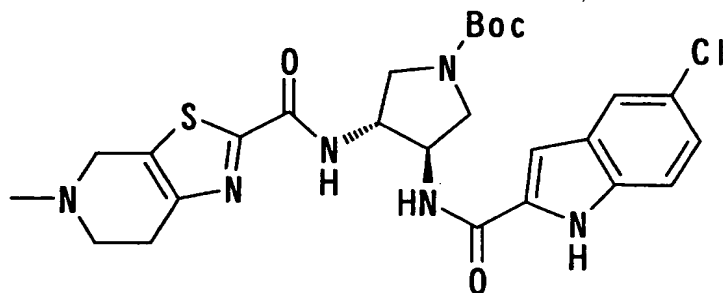


The title compound was obtained from the compound obtained in Referential Example 187 in accordance with the processes of Referential Example 172 and Example 91.

¹H-NMR and MS (FAB): The same as those of the enantiomer in Example 92.

[Example 94]

tert-Butyl (3R,4R)-3-[[[(5-chloroindol-2-yl)carbonyl]-amino]-4-[[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino]pyrrolidine-1-carboxylate:



The title compound was obtained from the compound obtained in Referential Example 193 and the compound obtained in Referential Example 10 in accordance with the process of Example 91.

Melting point: 190-192°C.

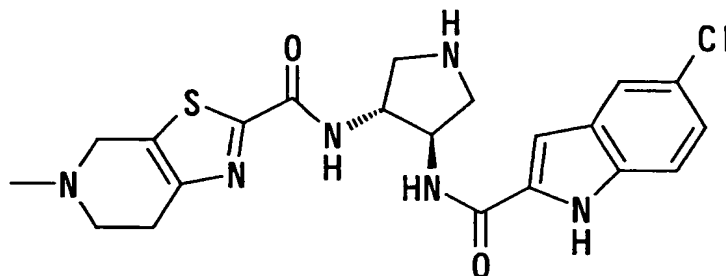
¹H-NMR (CDCl₃) δ: 1.45(9H,s), 2.46(3H,s), 2.74-2.81(4H,m),

3.24-3.37 (2H,m), 3.54-3.70 (2H,m), 3.96-4.00 (1H,m), 4.15-4.23 (1H,m), 4.50-4.65 (1H,m), 4.77-4.82 (1H,m), 6.79,6.87 (total 1H,each s), 7.12-7.95 (5H,m), 9.91,9.97 (total 1H,each s).

5 MS (FAB) m/z: 559 (M+H⁺).

[Example 95]

N-((3R,4R)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-pyrrolidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide hydrochloride:



10

The compound (170 mg) obtained in Example 94 was dissolved in methylene chloride (3 ml), and trifluoroacetic acid (2 ml) was added at room temperature to stir the mixture for 1 hour. After concentrating the reaction mixture, chloroform and a saturated aqueous solution of sodium hydrogencarbonate were added. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by preparative thin-layer chromatography on silica gel (chloroform:methanol:water = 7:3:1 under layer). A methanol solution of hydrochloric acid was added to the

15

20

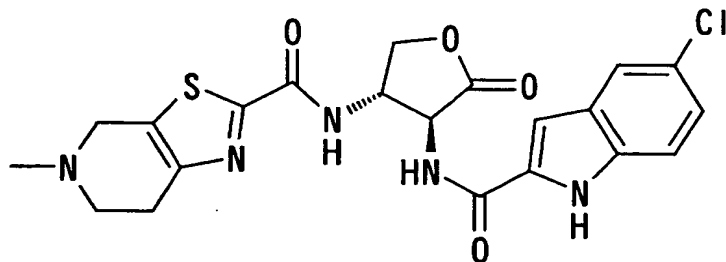
resultant intended product to obtain the title compound (90 mg) as a hydrochloride (NMR was measured in the form of a free base).

Melting point: 248-250°C (decomposed).

5 ¹H-NMR (CDCl₃) δ: 2.44 (3H, s), 2.70-2.80 (4H, m), 2.97-3.05 (2H, m), 3.46-3.68 (4H, m), 4.49-4.52 (1H, m), 4.60-4.65 (1H, m), 6.86 (1H, s), 7.05-7.08 (1H, m), 7.20 (1H, d, J=8.5 Hz), 7.44 (1H, s), 7.89 (2H, br), 10.51 (1H, br).
MS (FAB) m/z: 459 (M+H⁺).

10 [Example 96]

N-((3S,4S)-4-[[(5-Chloroindol-2-yl) carbonyl] amino]-5-oxotetrahydrofuran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



15 The title compound was obtained by removing the tert-butoxycarbonyl group of the compound obtained in Referential Example 196 in a similar manner to Referential Example 69 and reacting the resultant product with the compound obtained in Referential Example 10 in a similar
20 manner to Example 91.

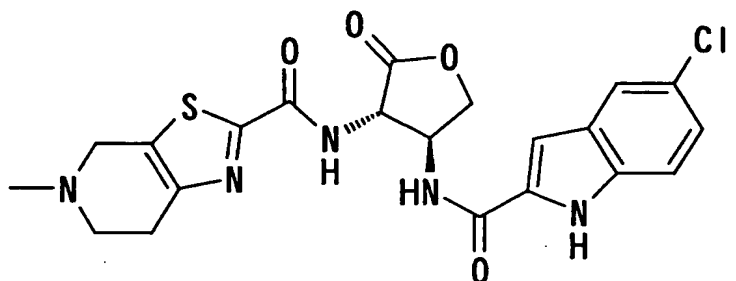
¹H-NMR (DMSO-d₆) δ: 2.90 (3H, s), 3.02-3.17 (2H, m), 3.23-3.34 (4H, m), 4.20 (1H, t, J=8.6 Hz), 4.61 (1H, t, J=8.6 Hz), 4.92-

5.01(1H,m), 5.14-5.26(1H,m), 7.09(1H,s),
7.19(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz),
7.73(1H,d,J=2.0Hz), 9.27(1H,d,J=6.8Hz), 9.35(1H,d,J=6.8Hz),
11.22-11.33(1H,m), 11.89(1H,s).

5 MS (FAB) m/z: 474 (M+H⁺).

[Example 97]

N-((3S,4S)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-2-oxotetrahydrofuran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



10

The title compound was obtained by removing the tert-butoxycarbonyl group of the compound obtained in Referential Example 197 in a similar manner to Referential Example 69 and reacting the resultant product with 5-chloroindole-2-carboxylic acid in a similar manner to Example 91.

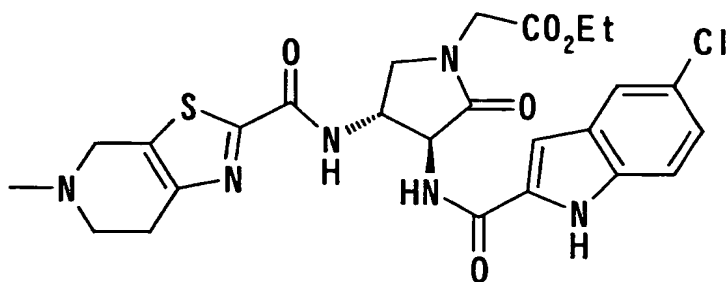
¹H-NMR (DMSO-d₆) δ: 2.52(3H,s), 2.83(2H,t,J=5.9Hz), 2.91-3.00(2H,m), 3.73(2H,s), 4.23(1H,t,J=8.6Hz), 4.40-4.53(1H,m), 4.96(1H,dd,J=10.8,5.2Hz),
20 5.16(1H,dd,J=9.2,7.3Hz), 7.01(1H,s),
7.25(1H,dd,J=8.8,2.0Hz), 7.34(1H,d,J=8.8Hz),
7.52(1H,d,J=2.0Hz), 8.01(1H,d,J=5.4Hz), 8.51-

8.63 (1H, m), 9.22 (1H, s).

MS (FAB) m/z: 474 (M+H⁺).

[Example 98]

Ethyl (3S,4R)-2-(3-{[(5-chloroindol-2-yl)carbonyl]amino}-
5 4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}-2-oxopyrrolidin-1-yl)acetate
hydrochloride:

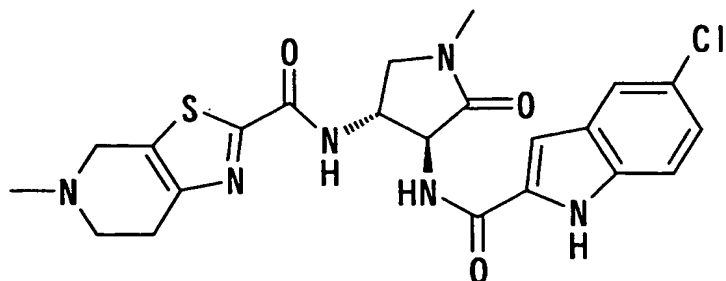


The title compound was obtained from the compound
10 obtained in Referential Example 199 and the compound
obtained in Referential Example 10 in a similar manner to
Example 91. NMR was measured in the form of a free base.
¹H-NMR (DMSO-d₆) δ: 1.19 (3H, t, J=7.1 Hz), 2.35 (3H, s), 2.71-
2.84 (2H, m), 2.80-2.90 (2H, m), 3.40 (1H, d, J=10.3 Hz),
15 3.61 (2H, d, J=10.8 Hz), 3.84 (1H, dd, J=10.3, 5.6 Hz), 4.01-
4.23 (4H, m), 4.80-4.94 (1H, m), 5.04 (1H, t, J=8.6 Hz),
7.01 (1H, s), 7.16 (1H, dd, J=8.8, 2.0 Hz), 7.40 (1H, d, J=8.8 Hz),
7.69 (1H, d, J=2.0 Hz), 8.73 (1H, d, J=8.6 Hz), 8.90 (1H, d, J=8.8 Hz),
11.86 (1H, s).
20 MS (FAB) m/z: 559 (M+H⁺).

[Example 99]

N-((3R,4S)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-

methyl-5-oxopyrrolidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



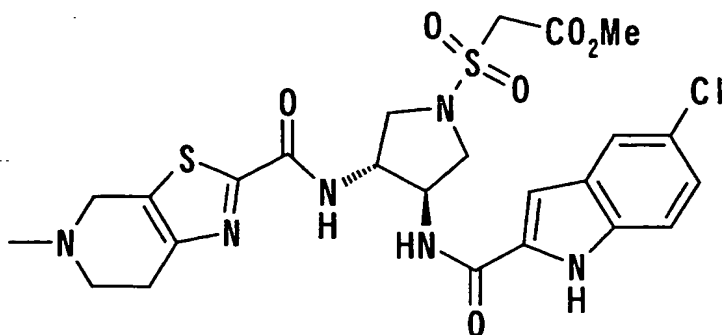
The title compound was obtained from the compound
 5 obtained in Referential Example 201 and the compound
 obtained in Referential Example 10 in a similar manner to
 Example 91.

¹H-NMR (CDCl₃) δ: 2.49(3H,s), 2.77-2.82(2H,m), 2.86-
 2.91(5H,m), 3.69(2H,d,J=1.2Hz), 4.39-4.54(3H,m), 4.93-
 10 4.98(1H,m), 6.98(1H,d,J=1.2Hz), 7.05-7.34(3H,m),
 7.63(1H,d,J=2.0Hz), 8.11(1H,d,J=7.8Hz), 9.00(1H,s)

MS (FAB) m/z: 487(M+H⁺).

[Example 100]

Methyl 2-(((3R,4R)-3-(((5-chloroindol-2-yl)carbonyl)-
 15 amino)-4-(((5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
 pyridin-2-yl)carbonyl)amino)pyrrolidin-1-yl)-
 sulfonyl]acetate:



The compound (230 mg) obtained in Example 95 and triethylamine (0.10 ml) were dissolved in methylene chloride (6.9 ml), and the mixture was cooled with ice.

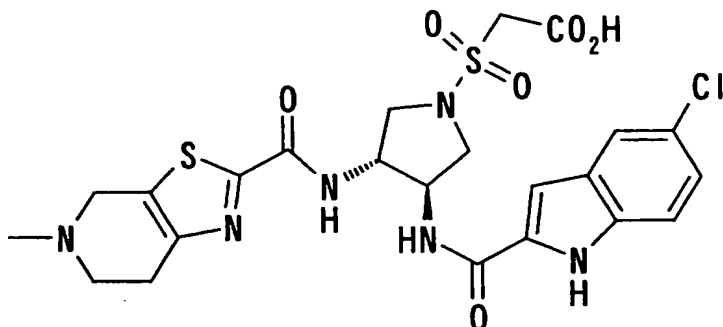
5 Methoxycarbonylmethanesulfonyl chloride (Synthesis, p. 321, 1975) (105 mg) was added, and the resultant mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with chloroform, washed with water and saturated aqueous solution of sodium chloride
 10 and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by preparative thin-layer chromatography on silica gel (chloroform:methanol = 20:1) and powdered with methanol-water to obtain the title
 15 compound (150 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.48(3H,s), 2.76-2.86(4H,m), 3.49-3.73(4H,m), 3.87(3H,s), 3.94-3.98(1H,m), 4.08-4.11(1H,m), 4.13(2H,s), 4.69-4.72(1H,m), 4.88-4.91(1H,m), 6.89(1H,s),
 7.12-7.15(1H,m), 7.27-7.28(1H,m), 7.50(1H,s), 7.81-
 20 7.86(2H,m), 9.92(1H,s).

MS (FAB) m/z : 595($\text{M}+\text{H}^+$).

[Example 101]

2-[(3R,4R)-3-[[5-chloroindol-2-yl]carbonyl]amino]-4-
[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl]carbonyl]amino]pyrrolidin-1-yl)sulfonyl]acetic acid:



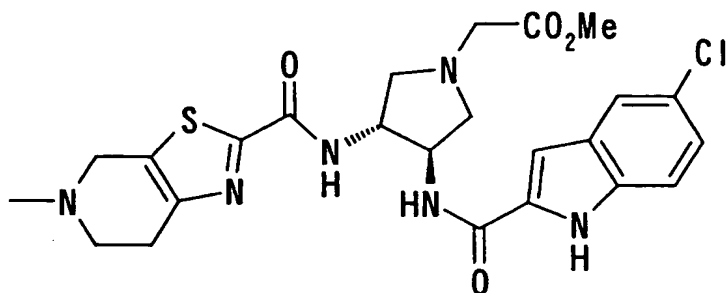
5

The compound (100 mg) obtained in Example 100 was dissolved in tetrahydrofuran (4 ml)-water (1 ml), and the mixture was cooled with ice. Lithium hydroxide monohydrate (7.8 mg) was added, and the resultant mixture was heated to room temperature and stirred for 4 hours. After the reaction mixture was neutralized with 1N hydrochloric acid, it was concentrated. Deposits were collected by filtration, washed with water and 50% ethanol and dried overnight at 50°C under reduced pressure to obtain the title compound (87 mg).

¹H-NMR (DMSO-d₆) δ: 2.50 (3H, s), 2.92 (4H, s), 3.34-3.43 (4H, m), 3.76-3.85 (2H, m), 4.27 (each 1H, AB type d, J=14.5 Hz), 4.65-4.71 (1H, m), 4.78-4.84 (1H, m), 7.14 (1H, s), 7.18 (1H, d, J=8.8 Hz), 7.40 (1H, d, J=8.8 Hz), 7.72 (1H, s), 8.87 (1H, d, J=7.8 Hz), 9.12 (1H, d, J=8.2 Hz), 11.83 (1H, s).

[Example 102]

Methyl 2-((3R,4R)-3-[[(5-chloroindol-2-yl) carbonyl]-amino]-4-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl) carbonyl]amino)pyrrolidin-1-yl)acetate:



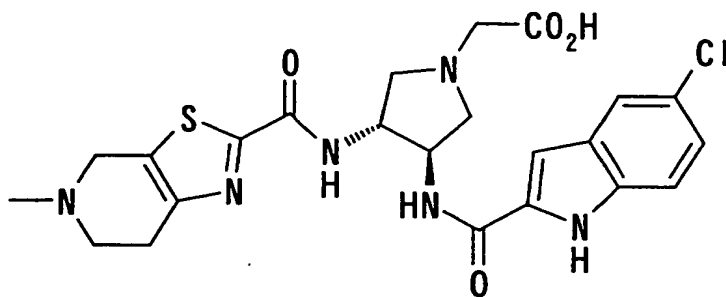
5 The compound (230 mg) obtained in Example 95 and potassium carbonate (90 mg) were dissolved in N,N-dimethylformamide (4.6 ml), and the mixture was cooled with ice. Methyl bromoacetate (0.062 ml) was added, and the resultant mixture was stirred for 45 minutes. The
10 reaction mixture was diluted with ethyl acetate, washed with water and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by preparative thin-layer
15 chromatography on silica gel (chloroform:methanol = 10:1) and solidified with methanol-water to obtain the title compound (190 mg).

¹H-NMR (CDCl₃) δ: 2.35(2H,s), 2.48(3H,s), 2.73-2.95(4H,m), 3.34-3.42(2H,m), 3.46(2H,q,J=6.5Hz), 3.67(2H,q,J=6.5Hz),
20 3.75(3H,s), 4.57-4.71(2H,m), 6.91(1H,s), 7.10-7.13(1H,m), 7.31(1H,d,J=9.0Hz), 7.53(1H,s), 7.77(1H,d,J=8.0Hz), 7.87(1H,d,J=6.8Hz), 10.22(1H,s).

MS (FAB) m/z : 531 ($M+H^+$).

[Example 103]

2-((3R,4R)-3-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)acetic acid:

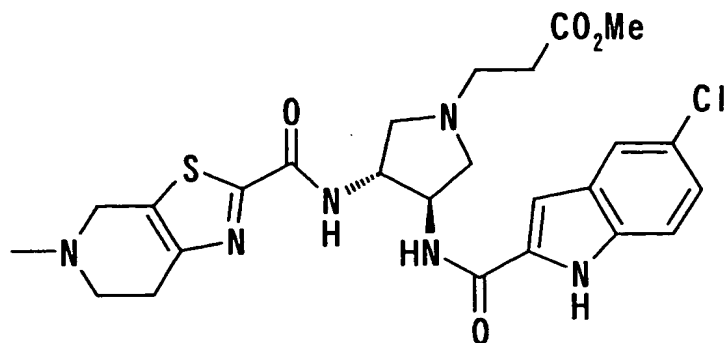


The title compound was obtained from the compound obtained in Example 102 in a similar manner to Example 101.

¹H-NMR (DMSO-d₆) δ : 2.42 (3H, s), 2.69-2.87 (6H, m),
3.13 (1H, t, J=9.0 Hz), 3.22 (1H, t, J=9.0 Hz), 3.33 (each 1H, AB
type d, J=6.8 Hz), 3.72 (2H, s), 4.53-4.60 (1H, m), 4.65-
4.72 (1H, m), 7.16-7.20 (2H, m), 7.42 (1H, d, J=8.8 Hz),
7.70 (1H, s), 8.85 (1H, d, J=7.5 Hz), 9.00 (1H, d, J=8.3 Hz),
11.79 (1H, s).

[Example 104]

Methyl 3-((3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)propionate:



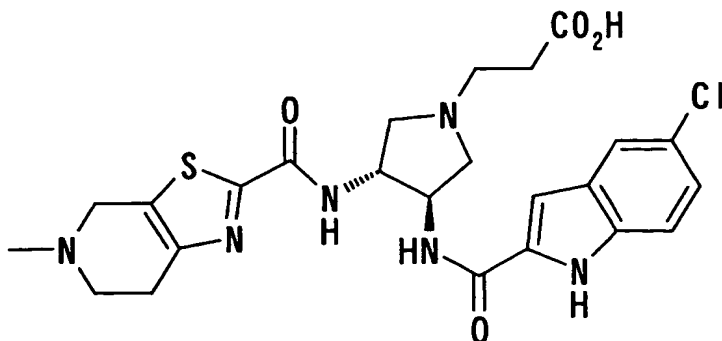
The title compound was obtained from the compound obtained in Example 95 and methyl 3-bromopropionate in a similar manner to Example 102.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.96-2.20 (2H,m), 2.49 (3H,s), 2.61-2.96 (8H,m), 3.17-3.21 (2H,m), 3.62-3.72 (2H,m), 3.69 (3H,s), 4.46-4.49 (1H,m), 4.56-4.61 (1H,m), 6.87 (1H,s), 7.05-7.14 (1H,m), 7.32 (1H,d, $J=9.2\text{Hz}$), 7.53 (1H,s), 7.65-7.71 (2H,m), 10.02 (1H,s).

10 MS (FAB) m/z : 545 ($\text{M}+\text{H}^+$).

[Example 105]

3-((3R,4R)-3-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)propionic acid:

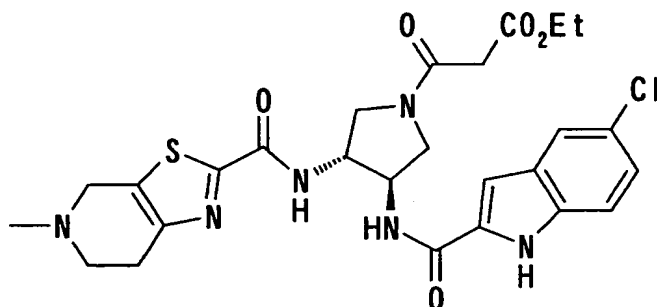


The title compound was obtained from the compound obtained in Example 104 in a similar manner to Example 101.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.38(3H,s), 2.39-2.84(10H,m),
2.93(1H,t,J=8.8Hz), 3.05(1H,t,J=8.8Hz), 3.65(2H,s), 4.51-
5 4.56(1H,m), 4.63-4.68(1H,m), 7.16-7.19(2H,m),
7.41(1H,d,J=8.8Hz), 7.69(1H,s), 8.81(1H,d,J=7.8Hz),
8.97(1H,d,J=8.3Hz), 11.75(1H,s).

[Example 106]

Ethyl 3-((3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]amino}-
10 4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)-3-oxopropionate:

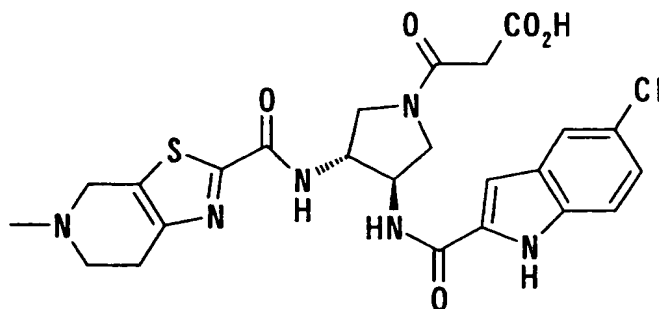


The title compound was obtained from the compound obtained in Example 95 and ethylmalonyl chloride in a
15 similar manner to Example 100.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.20(3H,t,J=7.0Hz), 2.37(3H,s), 2.73-
2.75(2H,m), 2.82-2.84(2H,m), 3.35-3.38(2H,m), 3.64(2H,s),
3.68-3.83(2H,m), 3.91-4.00(2H,m), 4.10(2H,q,J=7.0Hz),
4.61-4.84(2H,m), 7.13(1H,s), 7.18(1H,dd,J=8.5,2.0Hz),
20 7.41(1H,d,J=8.5Hz), 7.72(1H,s), 8.73(1H,t,J=9.0Hz),
9.10(1H,d,J=9.0Hz), 11.79(1H,s).

[Example 107]

3-((3R,4R)-3-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)-3-oxopropionic acid:



5

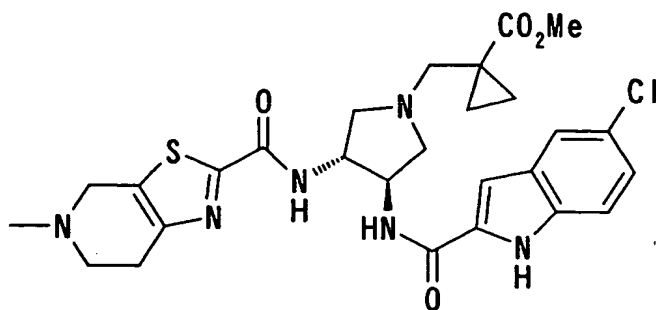
The title compound was obtained from the compound obtained in Example 106 in a similar manner to Example 101.

¹H-NMR (DMSO-d₆) δ: 2.39(3H,s), 2.77(2H,s), 2.85(2H,s), 3.29-3.55(4H,m), 3.68(2H,s), 3.82-4.01(2H,m), 4.62-4.68(1H,m), 4.77-4.86(1H,m), 7.14(1H,s), 7.18(1H,d,J=8.8Hz), 7.41(1H,d,J=8.8Hz), 7.72(1H,s), 8.75(1H,t,J=8.8Hz), 9.12(1H,d,J=7.8Hz), 11.81(1H,s).

[Example 108]

Methyl 1-[(3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)methyl]-cyclopropanecarboxylate:

15



The title compound was obtained from the compound obtained in Example 95 and methyl 1-(bromomethyl)-cyclopropanecarboxylate in a similar manner to Example 102.

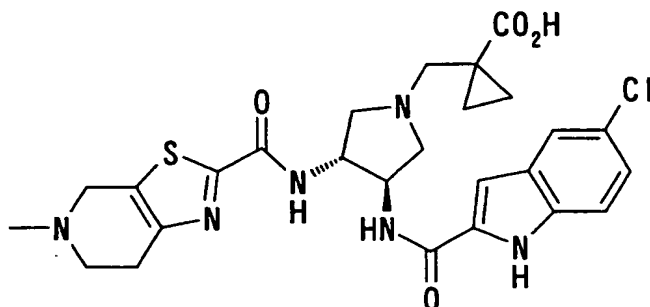
5 ¹H-NMR (CDCl₃) δ: 0.78-0.79 (2H, m), 1.24-1.26 (2H, m), 2.49 (3H, s), 2.62-2.88 (6H, m), 3.20-3.28 (2H, m), 3.66 (3H, s), 3.61-3.75 (4H, m), 4.45-4.62 (2H, m), 6.86 (1H, s), 7.12-7.15 (1H, m), 7.24-7.28 (1H, m), 7.52 (1H, d, J=8.5 Hz), 7.54 (1H, s), 7.69 (1H, d, J=8.0 Hz), 10.00 (1H, s).

10 MS (ESI) m/z: 571 (M+H⁺).

[Example 109]

1-(((3R,4R)-3-(((5-Chloroindol-2-yl)carbonyl)amino)-4-(((5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl)amino)pyrrolidin-1-yl)methyl)-

15 cyclopropanecarboxylic acid:

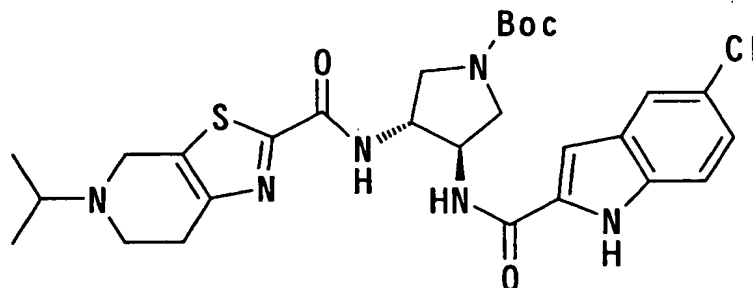


The title compound was obtained from the compound obtained in Example 108 in a similar manner to Example 101.

¹H-NMR (DMSO-d₆) δ: 0.73-0.78 (2H, m), 1.04-1.07 (2H, m),
 2.37 (3H, s), 2.65-2.84 (6H, m), 3.11-3.20 (4H, m), 3.64 (2H, s),
 4.59-4.74 (2H, m), 7.16 (1H, s), 7.17 (1H, d, J=8.5Hz),
 7.40 (1H, d, J=8.5Hz), 7.70 (1H, s), 8.84 (1H, d, J=7.5Hz),
 9.12 (1H, d, J=7.5Hz), 11.77 (1H, s).

[Example 110]

tert-Butyl (3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]-
 amino}-4-{[(5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
 pyridin-2-yl)carbonyl]amino}pyrrolidine-1-carboxylate:

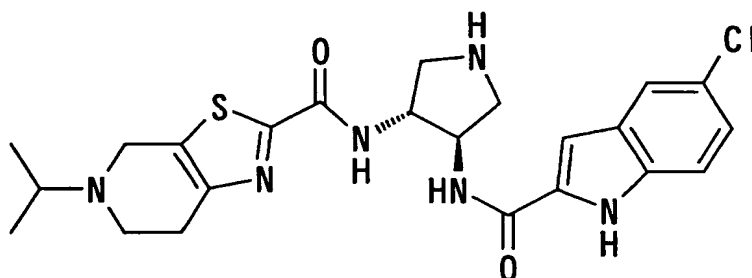


The title compound was obtained from the compound obtained in Referential Example 193 and Referential
 Example 148 in a similar manner to Example 91.

¹H-NMR (CDCl₃) δ: 1.12 (6H, d, J=6.6 Hz), 1.47 (9H, s), 2.83-2.88 (4H, m), 2.94-2.99 (1H, m), 3.20-3.29 (1H, m), 3.31-3.42 (1H, m), 3.75-3.81 (2H, m), 3.98 (1H, t, J=8.5 Hz), 4.15-4.35 (2H, m), 4.50-4.65 (1H, m), 6.85, 6.91 (total 1H, each s),
 5 7.15-7.90 (5H, m), 9.41, 9.50 (total 1H, each s).

[Example 111]

N-((3R,4R)-4-{[(5-chloroindol-2-yl)carbonyl]amino}pyrrolidin-3-yl)-5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



10

The title compound was obtained from the compound obtained in Example 110 in a similar manner to Example 95.

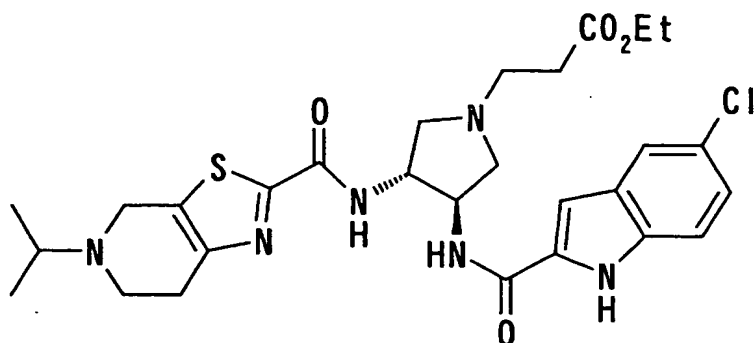
¹H-NMR (CDCl₃) δ: 1.13 (6H, d, J=6.3 Hz), 2.85 (4H, br. s), 2.96-3.05 (3H, m), 4.51-4.52 (1H, m), 4.76-4.80 (2H, m), 5.36-5.39 (2H, m), 5.53-5.58 (1H, m), 7.17-7.19 (1H, m), 7.27-7.31 (2H, m), 7.57 (1H, s), 7.64 (2H, br), 9.82 (1H, br).

15

[Example 112]

Ethyl 3-((3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]amino}-4-{[(5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)propionate:

20



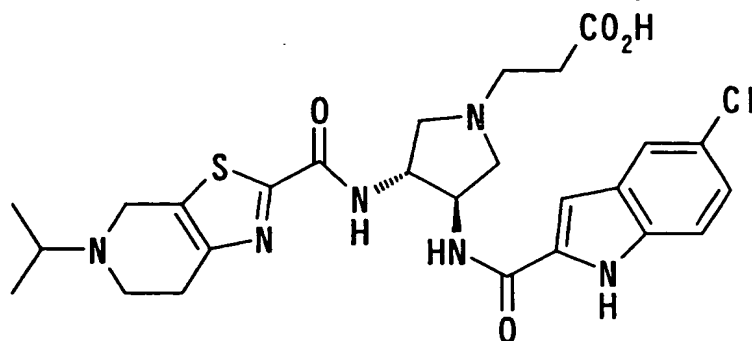
The title compound was obtained from the compound obtained in Example 111 and ethyl 3-bromopropionate in a similar manner to Example 102.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.14 (6H, d, $J=6.5\text{Hz}$), 1.26 (3H, t, $J=7.0\text{Hz}$), 2.51 (3H, t, $J=7.0\text{Hz}$), 2.63 (1H, dd, $J=9.5, 6.5\text{Hz}$), 2.73-2.91 (6H, m), 2.95-3.02 (1H, m), 3.22 (2H, q, $J=7.0\text{Hz}$), 3.81 (each 1H, AB type d, $J=14.5\text{Hz}$), 4.16 (2H, q, $J=7.0\text{Hz}$), 4.40-4.45 (1H, m), 4.52-4.59 (1H, m), 6.88 (1H, d, $J=2.0\text{Hz}$), 7.17-7.19 (1H, m), 7.30-7.32 (2H, m), 7.59 (1H, s), 7.62 (1H, s), 9.56 (1H, s).

MS (FAB) m/z : 587 ($\text{M}+\text{H}^+$).

[Example 113]

3-((3R,4R)-3-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-{[(5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)propionic acid:

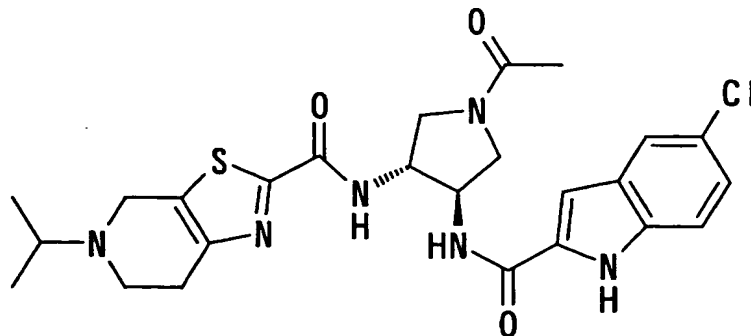


The title compound was obtained from the compound obtained in Example 112 in a similar manner to Example 101.

¹H-NMR (DMSO-d₆) δ: 1.04 (6H, d, J=6.6Hz), 2.40 (2H, q, J=7.0Hz),
 2.50 (4H, s), 2.60-2.74 (4H, m), 2.90-2.94 (2H, m), 3.02-
 3.06 (1H, m), 3.20-3.35 (2H, m), 4.50-4.53 (1H, m), 4.61-
 4.65 (1H, m), 7.15-7.18 (2H, m), 7.41 (1H, d, J=8.8Hz),
 7.68 (1H, s), 8.78 (1H, d, J=7.5Hz), 8.90 (1H, d, J=8.0Hz),
 11.73 (1H, s).

10 [Example 114]

N-((3R,4R)-1-Acetyl-4-[[(5-chloroindol-2-yl) carbonyl]-amino]pyrrolidin-3-yl)-5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



15 The title compound was obtained from the compound

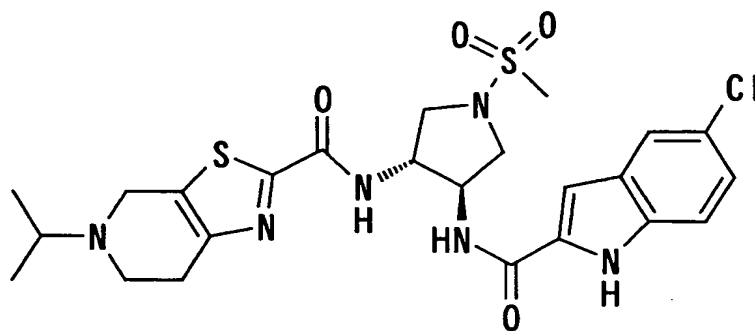
obtained in Example 111 and acetic anhydride in a similar manner to Example 100.

Melting point: 254-258°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.34-1.37(6H,m), 1.96(3H,s), 3.30-
5 3.55(5H,m), 3.66-3.82(3H,m), 3.95(1H,q,J=8.3Hz), 4.45-
4.82(4H,m), 7.15(1H,s), 7.18(1H,d,J=9.0Hz),
7.41(1H,d,J=9.0Hz), 7.71(1H,s), 8.75-8.81(1H,m),
9.21(1H,d,J=8.0Hz), 11.32(1H,br), 11.83(1H,d,J=7.3Hz).
MS (FAB) m/z: 529(M+H⁺).

10 [Example 115]

N-[(3R,4R)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(methylsulfonyl)pyrrolidin-3-yl]-5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



15

The title compound was obtained from the compound obtained in Example 111 and methanesulfonyl chloride in a similar manner to Example 100.

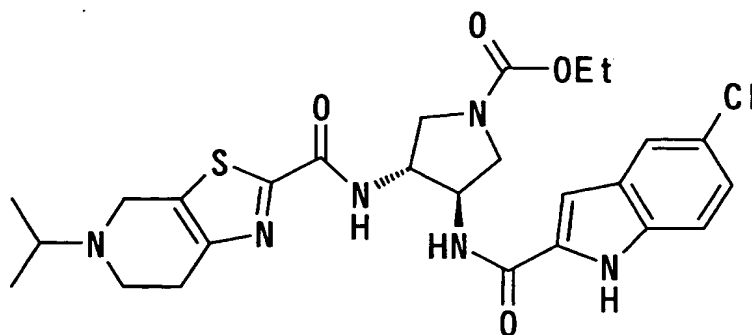
Melting point: 230-235°C (decomposed).

20 ¹H-NMR (DMSO-d₆) δ: 1.32-1.36(6H,m), 3.32(3H,s), 3.43-
3.46(5H,m), 3.68-3.75(4H,m), 4.48(1H,m), 4.62-4.72(2H,m),

4.83 (1H, t, J=5.5 Hz), 7.14 (1H, s), 7.18 (1H, d, J=8.6 Hz),
7.40 (1H, d, J=8.6 Hz), 7.72 (1H, s), 8.82 (1H, br),
9.20 (1H, d, J=8.3 Hz), 11.30 (1H, br), 11.86 (1H, d, J=7.5 Hz).
MS (FAB) m/z: 565 (M+H⁺).

5 [Example 116]

Ethyl (3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]amino}-4-
{[(5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]amino}pyrrolidine-1-carboxylate hydrochloride:



10 The title compound was obtained from the compound
obtained in Example 111 and ethyl chloroformate in a
similar manner to Example 100.

Melting point: 225-228°C (decomposed).

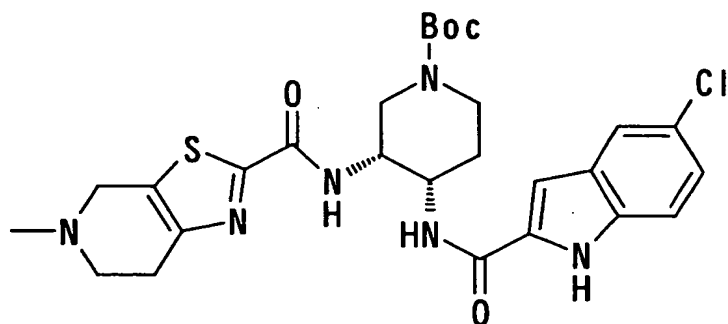
¹H-NMR (DMSO-d₆) δ: 1.20 (3H, t, J=7.0 Hz), 1.31-1.37 (6H, m),
15 3.33-3.45 (5H, m), 3.66-3.75 (4H, m), 4.05 (2H, q, J=7.0 Hz),
4.45-4.77 (4H, m), 7.15 (1H, s), 7.17 (1H, dd, J=8.8, 2.0 Hz),
7.41 (1H, d, J=8.8 Hz), 7.71 (1H, d, J=2.0 Hz), 8.77 (1H, d, J=7.0 Hz),
9.20 (1H, d, J=8.0 Hz), 11.30 (1H, br), 11.83 (1H, d, J=7.5 Hz).

MS (FAB) m/z: 559 (M+H⁺).

20 [Example 117]

tert-Butyl (3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]-

amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate:



The title compound was obtained from the compound
 5 obtained in Referential Example 207 and Referential
 Example 10 in a similar manner to Example 91.

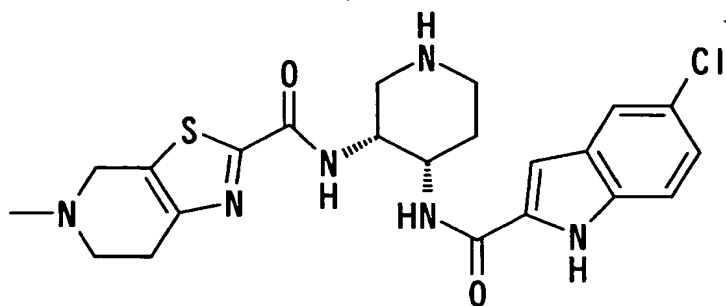
Melting point: 152-154°C (decomposed).

¹H-NMR (CDCl₃) δ: 1.53(9H,s), 1.62-1.80(1H,m), 2.23-
 2.30(1H,m), 2.52(3H,s), 2.75-3.05(5H,m), 3.10-3.25(1H,m),
 10 3.68-3.82(2H,m), 4.15-4.45(4H,m), 6.89(1H,s),
 7.19(1H,dd,J=8.8,1.8Hz), 7.32(1H,d,J=8.8Hz),
 7.92(1H,d,J=1.8Hz), 7.75(1H,br.s), 8.21(1H,br.s),
 9.39(1H,s).

MS (ESI) m/z: 573(M+H)⁺.

15 [Example 118]

N-((3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-
 piperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-
 c]pyridine-2-carboxamide dihydrochloride:

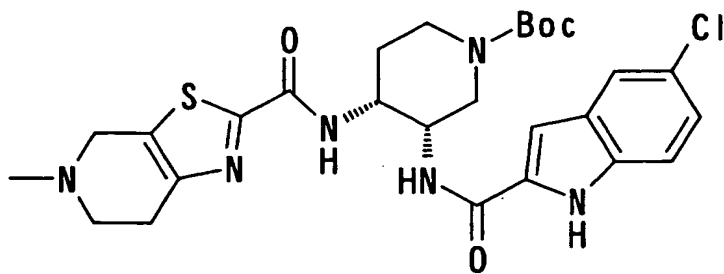


The title compound was obtained from the compound obtained in Example 117 in a similar manner to Example 95. Melting point: 240-258°C (decomposed).

- 5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.85-2.00 (1H,m), 2.05-2.20 (2H,m), 2.93 (3H,s), 3.05-3.60 (7H,m), 3.65-3.75 (1H,m), 4.10-4.52 (2H,m), 4.60-4.75 (2H,m), 7.10-7.21 (2H,m), 7.43 (1H,d,J=8.6Hz), 7.70 (1H,s), 8.50 (1H,br.d,J=7.8Hz), 8.90-9.05 (2H,m), 9.27 (1H,br.s), 11.9 (1H,br.d,J=13.4Hz).
- 10 MS (ESI) m/z : 473 ($\text{M}+\text{H}$) $^+$.

[Example 119]

tert-Butyl (3R*,4S*)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate:



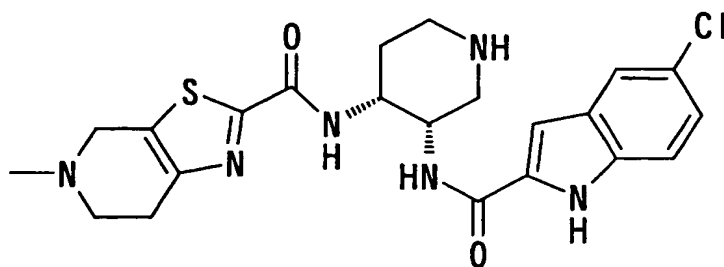
The title compound was obtained from the compound obtained in Referential Example 208 and 5-chloroindole-2-carboxylic acid in a similar manner to Example 91.

Melting point: 187-189°C (decomposed).

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (9H, s), 1.72-1.90 (1H, m),
2.00 (1H, br. s), 2.00-2.10 (1H, m), 2.45 (3H, s), 2.60-
2.70 (2H, m), 2.70-2.80 (2H, m), 3.23 (1H, t, $J=10.8\text{Hz}$), 3.35-
3.50 (1H, m), 3.50-3.72 (2H, m), 3.90-4.20 (2H, m), 4.30-
4.40 (1H, m), 4.45-4.55 (1H, m), 6.85 (1H, d, $J=1.5\text{Hz}$),
10 7.17 (1H, dd, $J=8.8, 1.9\text{Hz}$), 7.20-7.30 (1H, m),
7.33 (1H, d, $J=8.8\text{Hz}$), 7.58 (1H, d, $J=1.9\text{Hz}$), 10.17 (1H, s).
MS (ESI) m/z : 573 ($\text{M}+\text{H}^+$).

[Example 120]

N-((3R*,4S*)-3-{[(5-Chloroindol-2-yl)carbonyl]amino}-
15 piperidin-4-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo-
[5,4-c]pyridine-2-carboxamide dihydrochloride:



The title compound was obtained from the compound obtained in Example 119 in a similar manner to Example 95.

20 Melting point: 276-278°C (decomposed).

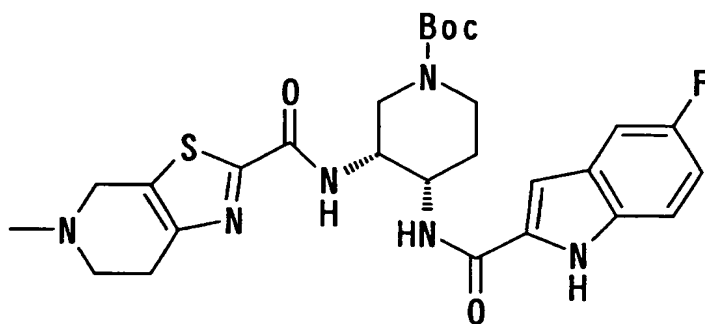
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.77-1.88 (1H, m), 2.40-2.50 (2H, m),
2.89 (3H, s), 2.90-3.20 (4H, m), 3.30-3.50 (2H, m),

3.63 (1H, br. s), 4.33-4.47 (2H, m), 4.62-4.75 (2H, m),
7.18 (1H, dd, J=8.8, 1.9 Hz), 7.42 (1H, d, J=8.8 Hz), 7.48 (1H, br. s),
7.71 (1H, d, J=1.9 Hz), 8.66 (1H, br. s), 8.95 (1H, d, J=8.1 Hz),
9.20-9.30 (1H, m), 9.45-9.70 (1H, m), 11.61 (1H, s), 11.90 (1H, s).

5 MS (ESI) m/z: 473 (M+H)⁺.

[Example 121]

tert-Butyl (3R*,4S*)-4-[[[(5-fluoroindol-2-yl)carbonyl]-
amino]-3-[[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridin-2-yl)carbonyl]amino]piperidine-1-carboxylate:



10

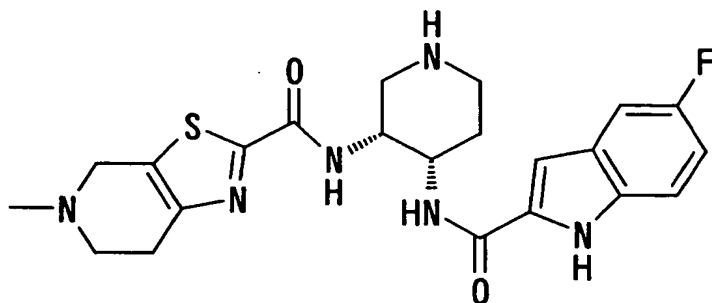
The title compound was obtained from the compound
obtained in Referential Example 209 and Referential
Example 10 in a similar manner to Example 91.

¹H-NMR (CDCl₃) δ: 1.53 (9H, s), 1.65-1.78 (1H, m), 2.23-
15 2.32 (1H, br), 2.52 (3H, s), 2.78-3.03 (5H, m), 3.15-3.24 (1H, br),
3.68-3.82 (2H, br), 4.16-4.45 (4H, br), 6.91 (1H, s),
7.02 (1H, td, J=9.0, 2.7 Hz), 7.30 (1H, dd, J=9.0, 2.7 Hz),
7.34 (1H, dd, J=9.0, 4.4 Hz), 7.65-7.90 (1H, br), 8.10-
8.40 (1H, br), 9.31-9.41 (1H, br).

20 MS (ESI) m/z: 557 (M+H)⁺.

[Example 122]

N-((3R*,4S*)-4-{[(5-Fluoroindol-2-yl)carbonyl]amino}-piperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide dihydrochloride:



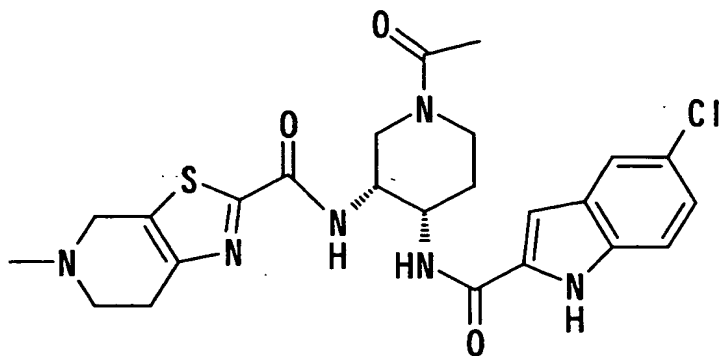
5 The title compound was obtained from the compound obtained in Example 121 in a similar manner to Example 95. Melting point: 236-245°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.85-1.98(1H,br), 2.06-2.18(1H,br), 2.89(3H,s), 3.05-3.75(8H,s), 4.34-4.54(2H,br), 4.60-
10 4.75(2H,br), 7.04(1H,td,J=9.3,2.4Hz), 7.15(1H,br.s), 7.37-7.44(2H,m), 8.46(1H,d,J=7.8Hz), 8.88-9.00(1H,br), 9.09-9.27(2H,br), 11.55-11.75(1H,br), 11.76-11.84(1H,br).

MS (FAB) m/z: 457 (M+H⁺).

[Example 123]

15 N-((3R*,4S*)-1-Acetyl-4-{[(5-chloroindol-2-yl)carbonyl]amino}piperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and acetic anhydride in a similar manner to Example 100.

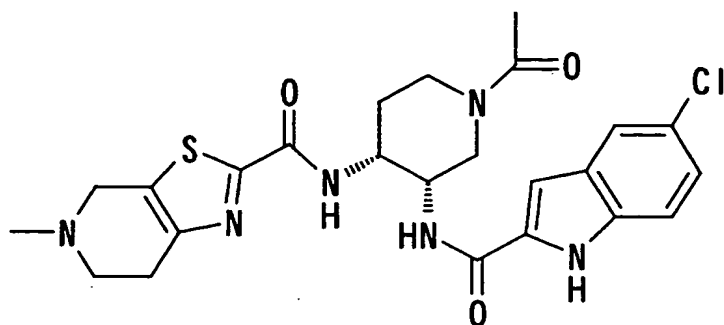
5 Melting point: 215-225°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.65-1.85(1H,m), 1.88,2.06(total 3H,each s), 1.90-2.10(1H,m), 2.91(3H,s), 3.00-3.30(2H,m), 3.30-3.55(2H,m), 3.60-3.90(3H,m), 3.98-4.50(4H,m), 4.65-4.75(1H,m), 7.09(1H,d,J=15.6Hz), 7.17(1H,d,J=8.8Hz), 7.41(1H,d,J=8.8Hz),7.71(1H,s), 8.23-8.53(2H,m), 11.20-11.55(1H,m), 11.85(1H,br.d,J=5.4Hz).

MS (ESI) m/z: 515(M+H⁺).

[Example 124]

N-((3R*,4S*)-1-Acetyl-3-(((5-chloroindol-2-yl)carbonyl)-amino)piperidin-4-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 120 and acetic anhydride in a similar manner to Example 100.

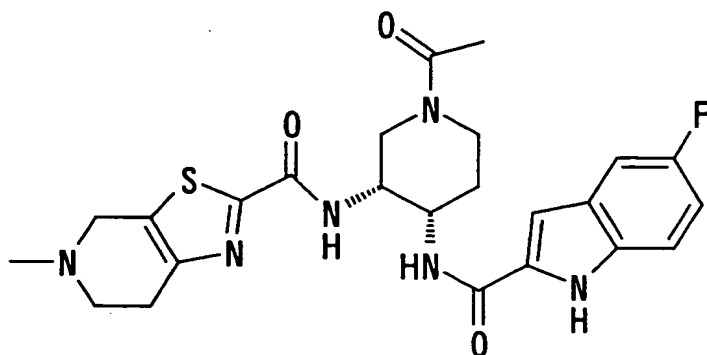
5 Melting point: 225-250°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.65-1.80 (1H,m),
 1.81,2.05 (total 3H,each s), 2.00-2.20 (1H,m), 2.70-
 2.85 (1H,m), 2.89 (3H,s), 3.00-3.20 (2H,m), 3.20-3.50 (2H,m),
 3.64 (1H,br.s), 3.78-4.30 (2H,m), 4.30-4.50 (3H,m), 4.55-
 10 4.75 (1H,m), 7.05-7.23 (2H,m), 7.38-7.48 (1H,m), 7.70-
 7.80 (1H,m), 7.79,8.12 (total 1H,each d,J=6.8Hz),
 8.73,8.83 (total 1H,each d,J=8.3Hz), 11.20-11.50 (1H,m),
 11.89,11.92 (total 1H,each s).

MS (FAB) m/z: 515 (M+H⁺).

15 [Example 125]

N-((3R*,4S*)-1-Acetyl-4-((5-fluoroindol-2-yl)carbonyl)-amino)piperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 122 and acetic anhydride in a similar manner to Example 100.

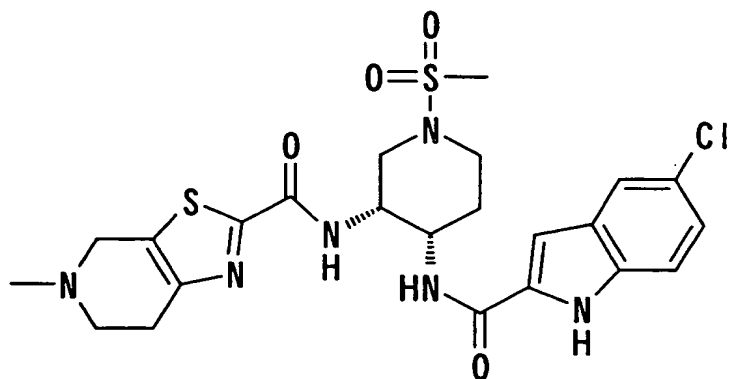
5 Melting point: 202°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.67-1.85(1H,m), 1.87(1.5H,s), 1.87-2.10(1H,m), 2.06(1.5H,s), 2.88-2.96(3H,br.s), 3.05-3.30(2H,m), 3.32-3.83(5H,br), 3.97-4.33(2H,m), 4.35-4.50(2H,br), 4.67-4.78(1H,br), 7.01-7.14(2H,m), 7.38-7.44(2H,m), 8.25-8.50(2H,m), 10.85-11.15(1H,br), 11.72-11.80(1H,br).

MS (FAB) m/z: 499(M+H⁺).

[Example 126]

15 N-[(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(methylsulfonyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and methanesulfonyl chloride in a similar manner to Example 100.

5 Melting point: 225-230°C (decomposed).

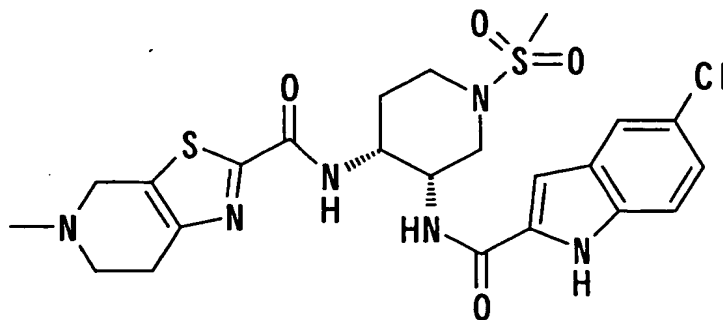
¹H-NMR (DMSO-d₆) δ: 1.80-1.90 (1H,m), 2.05-2.15 (1H,m), 2.30-2.80 (5H,m), 2.85-3.80 (9H,m), 4.20-4.90 (4H,m), 7.08 (1H,d,J=1.7Hz), 7.18 (1H,dd,J=8.7,1.7Hz), 7.42 (1H,d,J=8.7Hz), 7.77 (1H,s), 8.02-8.20 (1H,m), 8.40-8.50 (1H,m), 11.00-11.60 (1H,m), 11.87 (1H,s).

MS (ESI) m/z: 551 (M+H⁺).

[Example 127]

N-[(3R*,4S*)-3-{{(5-Chloroindol-2-yl)carbonyl}amino}-1-(methylsulfonyl)piperidin-4-yl]-5-methyl-4,5,6,7-

15 tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 120 and methanesulfonyl chloride in a similar manner to Example 100.

5 Melting point: 228-245°C (decomposed).

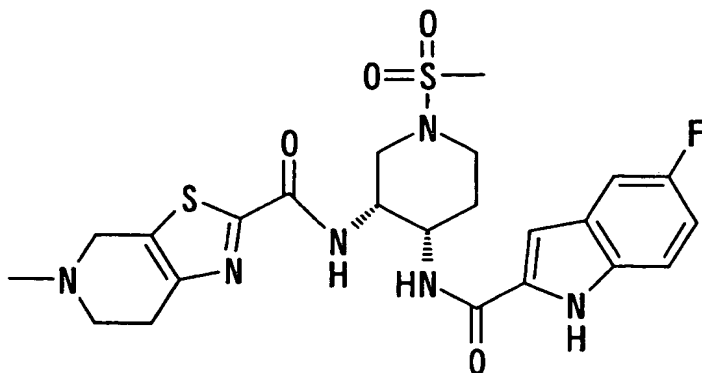
¹H-NMR (DMSO-d₆) δ: 1.75-1.85 (1H,m), 2.25-2.40 (1H,m), 2.40-2.60 (2H,m), 2.76 (3H,br.s), 2.90 (3H,s), 2.93-3.05 (3H,m), 3.12 (1H,d,J=10.6Hz), 3.55-3.80 (2H,m), 4.25-4.40 (4H,m), 7.17 (1H,d,J=1.7Hz), 7.19 (1H,dd,J=8.7,2.0Hz),

10 7.43 (1H,d,J=8.7Hz), 7.74 (1H,d,J=2.0Hz), 8.03 (1H,d,J=6.6Hz), 8.78 (1H,d,J=7.4Hz), 10.90-11.20 (1H,br.s), 11.89 (1H,s).

MS (ESI) m/z: 551 (M+H⁺).

[Example 128]

N-[(3R*,4S*)-4-[[(5-Fluoroindol-2-yl)carbonyl]amino]-1-(methysulfonyl)piperazin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 122 and methanesulfonyl chloride in a similar manner to Example 100.

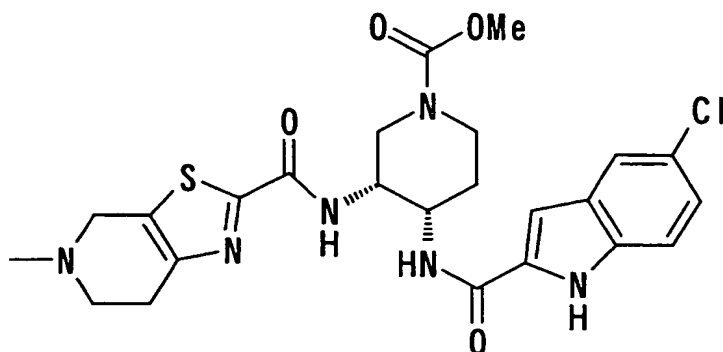
5 Melting point: 216-250°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.80-1.90 (1H,m), 2.01-2.12 (1H,m),
2.92 (3H,s), 2.94 (3H,s), 3.00-3.80 (8H,m), 4.28-4.53 (3H,m),
4.60-4.80 (1H,br), 7.01-7.12 (2H,m), 7.37-7.44 (2H,m), 8.00-
8.18 (1H,br), 8.39-8.50 (1H,br), 11.00-11.60 (1H,br), 11.72-
10 11.80 (1H,br).

MS (FAB) m/z: 535 (M+H⁺).

[Example 129]

Methyl (3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-
3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
15 yl)carbonyl]amino}piperidine-1-carboxylate hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and methyl chloroformate in a similar manner to Example 100.

5 Melting point: 248-253°C (decomposed).

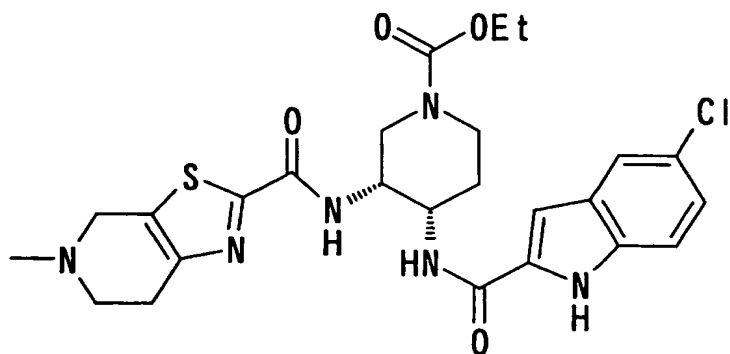
¹H-NMR (DMSO-d₆) δ: 1.65-1.78(1H,m), 1.88-2.03(1H,m),
2.90(3H,s), 3.00-3.80(9H,m), 3.80-3.90(1H,m), 3.95-
4.08(1H,m), 4.20-4.70(4H,m), 7.10(1H,s),
7.17(1H,dd,J=8.8,1.8Hz), 7.42(1H,d,J=8.8Hz),

10 7.71(1H,d,J=1.8Hz), 8.29(1H,br.s), 8.41(1H,d,J=8.1Hz),
11.29(1H,br.s), 11.85(1H,s).

MS (ESI) m/z: 531(M+H⁺).

[Example 130]

Ethyl (3R*,4S*)-4-{{[(5-chloroindol-2-yl)carbonyl]amino}-3-
15 {{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
yl)carbonyl]amino}piperidine-1-carboxylate hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and ethyl chloroformate in a similar manner to Example 100.

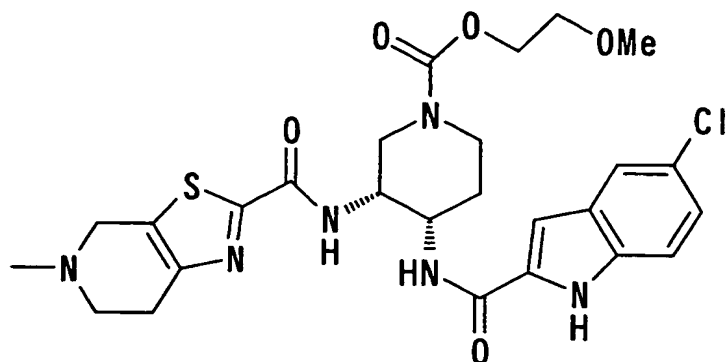
5 Melting point: 215-225°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 0.85-1.30 (3H,m), 1.65-1.78 (1H,m), 1.90-2.03 (1H,m), 2.90 (3H,s), 3.10-3.40 (4H,m), 3.48 (1H,br.s), 3.65 (1H,br.s), 3.75-4.15 (4H,m), 4.25 (1H,br.s), 4.32-4.50 (2H,m), 4.66 (1H,br.s), 7.09 (1H,s), 7.18 (1H,dd,J=8.8,2.0Hz), 7.41 (1H,d,J=8.8Hz), 7.71 (1H,d,J=2.0Hz), 8.23 (1H,br.s), 8.45 (1H,br.d,J=8.1Hz), 11.50 (1H,br.s), 11.86 (1H,s).

MS (ESI) m/z: 545 (M+H⁺).

[Example 131]

15 2-Methoxyethyl (3R*,4S*)-4-{[(5-chloroindol-2-yl)-carbonyl]amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and 2-methoxyethyl chloroformate in a similar manner to Example 100.

5 Melting point: 224-226°C (decomposed).

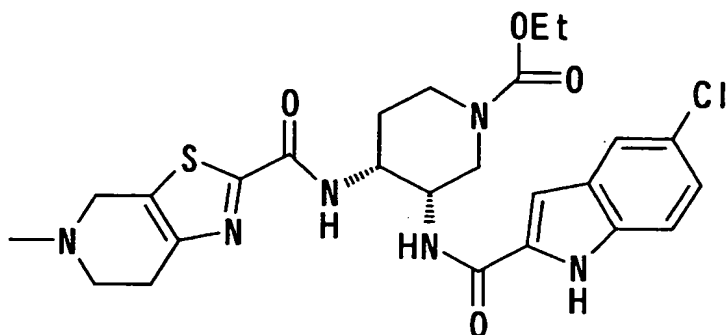
¹H-NMR (DMSO-d₆) δ: 1.68-1.78(1H,m), 1.90-2.03(1H,m), 2.89(3H,s), 3.00-3.75(11H,m), 3.80-3.90(1H,m), 3.95-4.18(3H,m), 4.20-4.70(4H,m), 7.10(1H,s), 7.17(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz),

10 7.71(1H,d,J=2.0Hz), 8.26(1H,br.s), 8.42(1H,d,J=7.8Hz), 11.30(1H,br.s), 11.86(1H,s).

MS (ESI) m/z: 575(M+H⁺).

[Example 132]

Ethyl (3R*,4S*)-3-{[(5-chloroindol-2-yl)carbonyl]amino}-4-
15 {[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate hydrochloride:



The title compound was obtained from the compound obtained in Example 120 and ethyl chloroformate in a similar manner to Example 100.

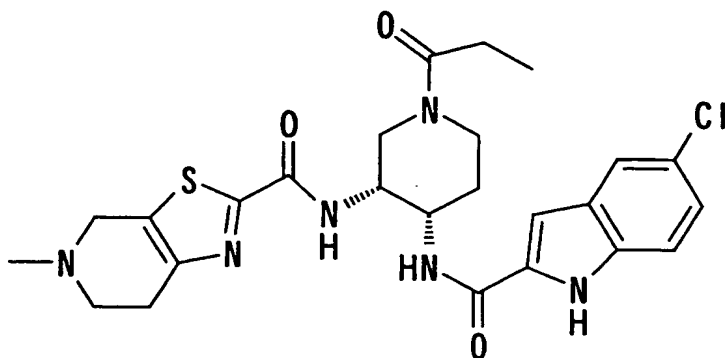
5 Melting point: 213-225°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 0.75-1.30 (3H, m), 1.60-1.72 (1H, m), 2.12-2.25 (1H, m), 2.89 (3H, s), 2.95-3.20 (4H, m), 3.40-3.88 (4H, m), 3.90-4.10 (2H, m), 4.10-4.30 (2H, m), 4.30-4.40 (1H, m), 4.40-4.80 (1H, m), 7.10 (1H, s), 7.18 (1H, dd, J=8.8, 2.0 Hz), 7.43 (1H, d, J=8.8 Hz), 7.74 (1H, s), 8.03 (1H, d, J=5.6 Hz), 8.79 (1H, s), 11.37 (1H, s), 11.88 (1H, s).

MS (ESI) m/z: 545 (M+H⁺).

[Example 133]

N-((3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-propionylpiperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and propionyl chloride in a similar manner to Example 100.

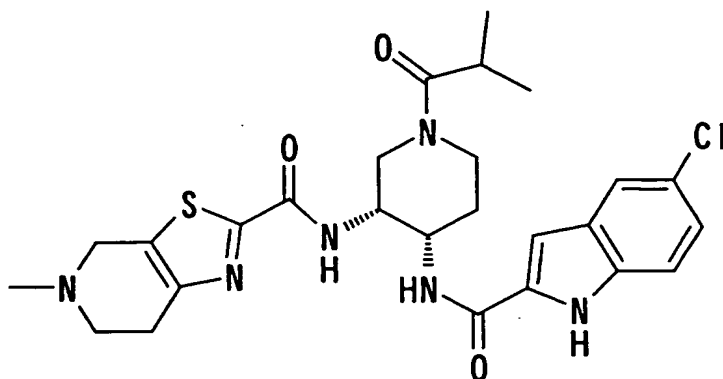
5 Melting point: 214-228°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 0.88-1.10(3H,m), 1.70-2.05(2H,m), 2.06-2.60(2H,m), 2.91(3H,s), 3.14(2H,br.s), 3.20-3.90(5H,m), 3.95-4.80(5H,m), 7.09(1H,d,J=11.0Hz), 7.17(1H,dd,J=8.8,1.2Hz), 7.41(1H,d,J=8.8Hz), 7.71(1H,s), 8.20-8.50(2H,m), 11.00-11.40(1H,m), 11.86(1H,s).

MS (ESI) m/z: 529(M+H⁺).

[Example 134]

N-((3R*,4S*)-4-{{[(5-Chloroindol-2-yl)carbonyl]amino}-1-isobutyrylpiperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and isobutyryl chloride in a similar manner to Example 100.

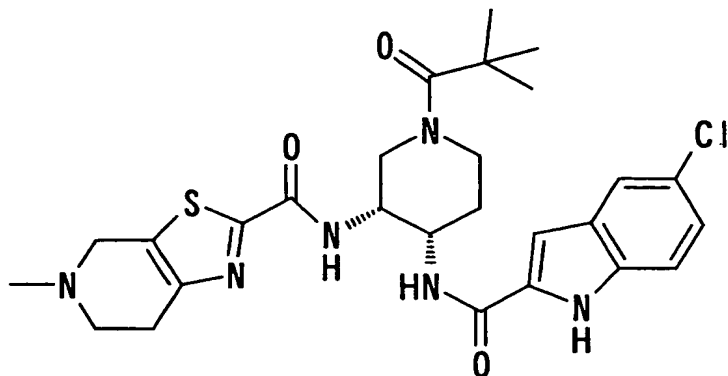
5 Melting point: 266-272°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 0.80-1.15(6H,m), 1.70-2.05(2H,m), 2.65-2.80(1H,m), 2.90(3H,s), 2.90-4.80(12H,m), 7.09(1H,d,J=11.0Hz), 7.17(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz), 7.71(1H,s), 8.00-8.30(1H,m), 8.30-8.50(1H,m), 10.95-11.50(1H,m), 11.86(1H,s).

MS (ESI) m/z: 543(M+H⁺).

[Example 135]

N-[(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(2,2-dimethylpropanoyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and pivaloyl chloride in a similar manner to Example 100.

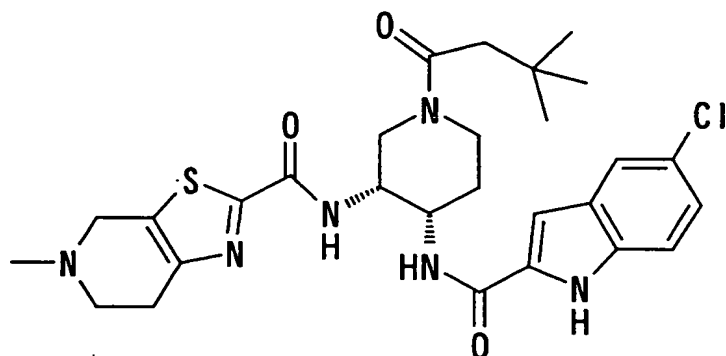
5 Melting point: 250-255°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.20(9H,s), 1.70-1.81(1H,m), 1.90-2.00(1H,m), 2.88(3H,s), 3.10(2H,br.s), 3.20-3.70(4H,m), 3.95-4.08(1H,m), 4.10-4.20(1H,m), 4.25-4.35(1H,m), 4.35-4.80(3H,m), 7.10(1H,s), 7.16(1H,dd,J=8.8,1.9Hz), 7.41(1H,d,J=8.8Hz), 7.69(1H,d,J=1.9Hz), 8.06(1H,br.s), 8.38(1H,d,J=7.8Hz), 11.31(1H,br.s), 11.84(1H,s).

MS (ESI) m/z: 557(M+H⁺).

[Example 136]

N-[(3R*,4S*)-4-{{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(3,3-dimethylbutanoyl)piperidin-3-yl}]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and tert-butylacetyl chloride in a similar manner to Example 100.

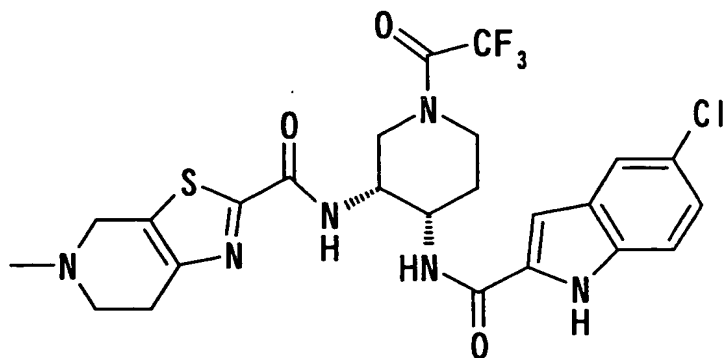
5 Melting point: 260-265°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 0.91, 1.04 (total 9H, each s), 1.68-1.82 (1H, m), 1.93-2.40 (3H, m), 2.91 (3H, s), 3.00-3.20 (2H, m), 3.20-4.80 (10H, m), 7.08 (1H, s), 7.17 (1H, dd, J=8.7, 1.2 Hz), 7.41 (1H, d, J=8.7 Hz), 7.69 (1H, d, J=7.6 Hz), 7.93-8.18 (1H, m), 8.38-8.45 (1H, m), 10.95-11.30 (1H, m), 11.80-11.90 (1H, m).

MS (ESI) m/z: 571 (M+H⁺).

[Example 137]

N-[(3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-(2,2,2-trifluoroacetyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and trifluoroacetic anhydride in a similar manner to Example 100.

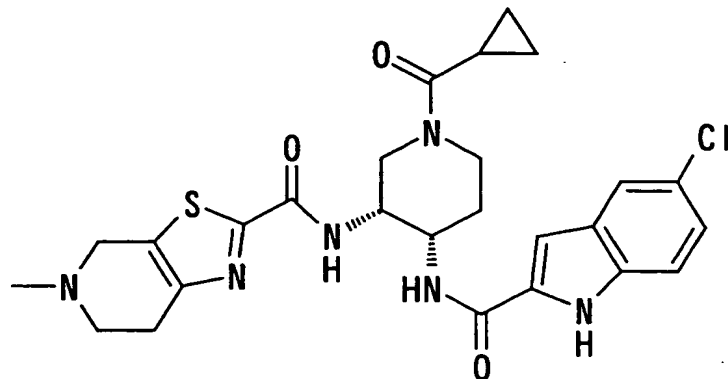
5 Melting point: 262-267°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.82-1.98(1H,m), 2.05-2.21(1H,m),
2.89(3H,s), 3.05-3.20(2H,m), 3.40-3.75(4H,m), 3.85-
3.95(1H,m), 4.00-4.07(1H,m), 4.20-4.70(4H,m), 7.10(1H,s),
7.18(1H,dd,J=8.6,1.9Hz), 7.41(1H,d,J=8.6Hz), 7.72(1H,s),
10 8.47(1H,dd,J=22.4,7.9Hz), 8.60(1H,br), 11.08(1H,br.s),
11.87(1H,s).

MS (ESI) m/z: 569(M+H⁺).

[Example 138]

N-[(3R*,4S*)-4-{{(5-Chloroindol-2-yl)carbonyl}amino}-1-(cyclopropylcarbonyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
15 hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and cyclopropanecarbonyl chloride in a similar manner to Example 100.

5 Melting point: 280-286°C (decomposed).

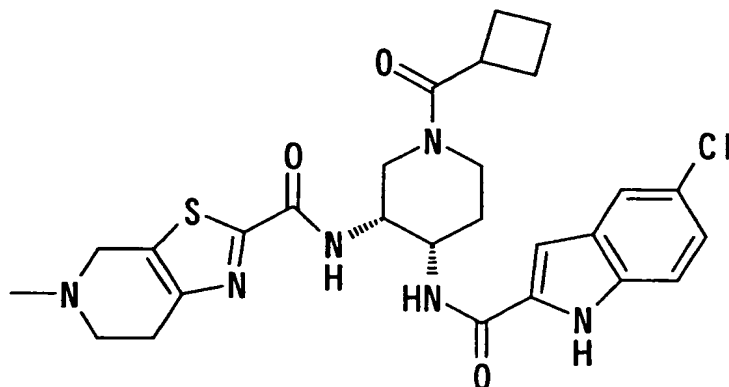
¹H-NMR (DMSO-d₆) δ: 0.25-0.80(4H,m), 1.65-2.15(4H,m),
2.91(3H,s), 2.90-3.20(3H,m), 3.35-3.70(2H,m), 4.00-
4.80(6H,m), 7.06(1H,s), 7.18(1H,d,J=8.8Hz),
7.42(1H,d,J=8.7Hz), 7.71(1H,s), 8.18(1H,br.s),

10 8.40,8.48(total 1H,each br.s), 11.11(1H,br.s), 11.85(1H,s).

MS (ESI) m/z: 542(M+H⁺).

[Example 139]

N-[(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(cyclobutylcarbonyl)piperidin-3-yl]-5-methyl-4,5,6,7-
15 tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and cyclobutanecarbonyl chloride in a similar manner to Example 100.

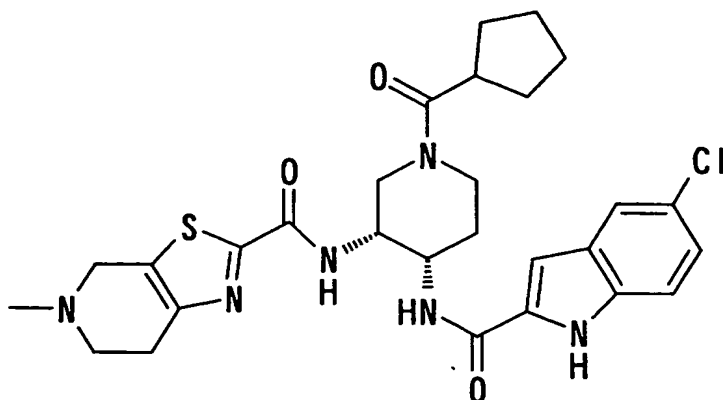
5 Melting point: 271-275°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.60-2.30 (8H,m), 2.89 (3H,s),
 3.12 (2H,br.s), 3.20-3.75 (6H,m), 3.75-3.90 (1H,m), 4.05-
 4.80 (4H,m), 7.08 (1H,s), 7.15 (1H,dd,J=9.0,2.0Hz),
 7.39 (1H,d,J=9.0Hz), 7.68 (1H,d,J=2.0Hz), 8.15 (1H,br.s),
 10 8.39 (1H,br), 11.19 (1H,br.s), 11.84 (1H,s).

MS (ESI) m/z: 555 (M+H⁺).

[Example 140]

N-[(3R*,4S*)-4-[[[(5-Chloroindol-2-yl)carbonyl]amino]-1-(cyclopentylcarbonyl)piperidin-3-yl]-5-methyl-4,5,6,7-
 15 tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
 hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and cyclopentanecarbonyl chloride in a similar manner to Example 100.

5 Melting point: 254-260°C (decomposed).

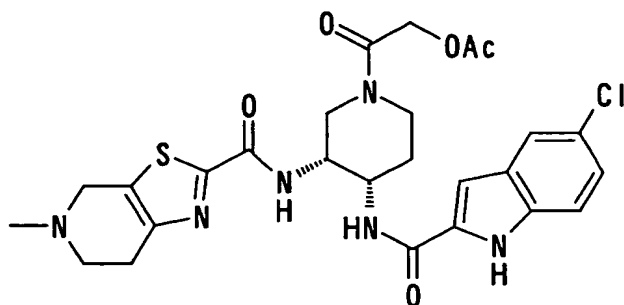
¹H-NMR (DMSO-d₆) δ: 1.30-2.10 (10H, m), 2.90 (3H, s), 3.00-3.20 (2H, m), 3.20-3.75 (5H, m), 3.80-4.80 (6H, m), 7.09 (1H, s), 7.17 (1H, dd, J=8.7, 2.0 Hz), 7.42 (1H, d, J=8.7 Hz), 7.71 (1H, s), 7.95-8.30 (1H, m), 8.35-8.50 (1H, m), 11.23 (1H, br. s),

10 11.85 (1H, s).

MS (ESI) m/z: 569 (M+H⁺).

[Example 141]

2-((3R*,4S*)-4-(((5-Chloroindol-2-yl)carbonyl)amino)-3-
 {[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-
 15 yl)carbonyl]amino}piperidin-1-yl)-2-oxoethyl acetate:



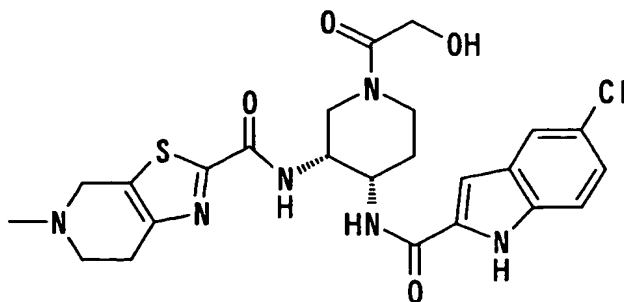
The title compound was obtained from the compound obtained in Example 118 and acetoxyacetyl chloride in a similar manner to Example 100.

5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.70-2.00 (1H, m), 2.05-2.48 (3H, m), 2.51 (3H, s), 2.70-3.05 (4H, m), 3.05-4.10 (5H, m), 4.20-4.48 (1H, m), 4.50-5.10 (4H, m), 6.87 (1H, br. s), 7.10-7.82 (4H, m), 7.32 (1H, d, $J=8.8\text{Hz}$), 8.35 (1H, br. s), 9.34, 9.45 (total 1H, each br. s).

10 MS (ESI) m/z : 573 ($M+H^+$).

[Example 142]

N-((3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-glycoloylpiperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



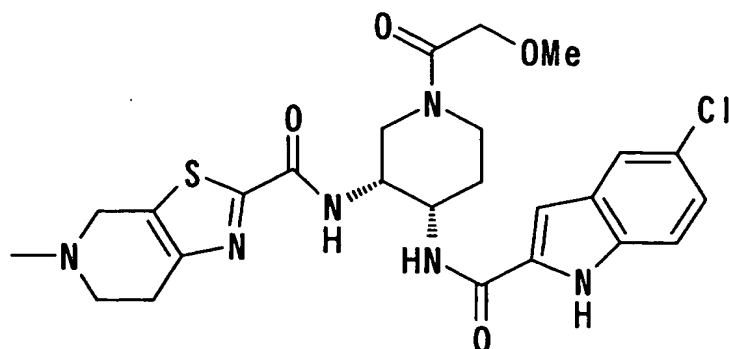
The compound (301.8 mg) obtained in Example 141 was dissolved in tetrahydrofuran (10 ml), and a 1N aqueous solution (0.53 ml) of sodium hydroxide was added to stir the mixture at room temperature for 18 hours. Water was added to the reaction mixture to conduct extraction with methylene chloride. The resultant organic layer was successively washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1 - 10:1), and the solvent was distilled off under reduced pressure. The thus-obtained purified product was dissolved in ethanol (3 ml) and methylene chloride (2 ml), and a 1N ethanol solution of hydrochloric acid to stir the mixture for 30 minutes. The solvent was distilled off under reduced pressure, and the residue was solidified with diethyl ether to obtain the title compound (195 mg). Melting point: 216-230°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.70-1.80(1H,m), 1.88-2.10(2H,m), 2.68(3H,s), 3.18(2H,s), 3.08-3.70(5H,m), 3.80-3.95(1H,m), 4.00-4.25(3H,m), 4.25-4.50(2H,m), 4.50-4.65(1H,m), 7.09(1H,d,J=11.0Hz), 7.17(1H,dd,J=8.8,2.0Hz), 7.42(1H,d,J=8.8Hz), 7.71(1H,s), 8.33(1H,br.s), 8.35-8.50(1H,m), 10.80-11.30(1H,br.s), 11.84(1H,br.s).

[Example 143]

N-[(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(2-

methoxyacetyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



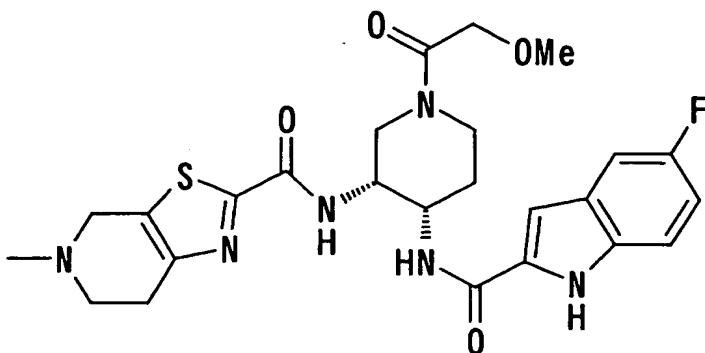
The title compound was obtained from the compound
 5 obtained in Example 118 in a similar manner to Example 100.
 Melting point: 214-228°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.70-1.80 (1H,m), 1.85-2.05 (1H,m),
 2.90 (3H,s), 3.00-3.20 (2H,m), 3.16 (3H,s), 3.22-3.82 (7H,m),
 3.88-4.80 (5H,m), 7.09 (1H,d,J=9.0Hz),
 7.17 (1H,dd,J=8.8,1.9Hz), 7.42 (1H,d,J=8.8Hz),
 7.70 (1H,d,J=1.9Hz), 8.29 (1H,br.s), 8.40-8.50 (1H,m),
 11.34 (1H,br.s), 11.86 (1H,s).

MS (ESI) m/z: 545 (M+H)⁺.

[Example 144]

15 N-[(3R*,4S*)-4-[[5-(5-Fluoroindol-2-yl)carbonyl]amino]-1-(2-methoxyacetyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 122 and methoxyacetyl chloride in a similar manner to Example 100.

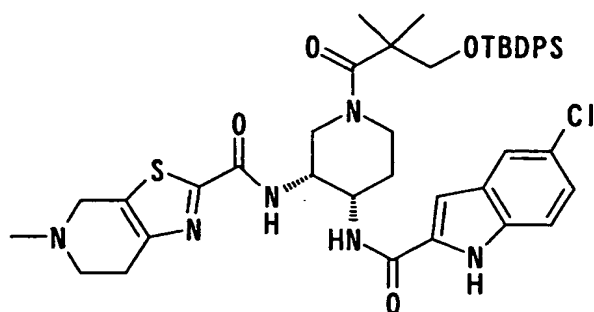
5 Melting point: 190-208°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.70-1.83(1H,br), 1.85-2.10(1H,m),
2.91(3H,s), 3.00-3.55(10H,m), 3.62-3.85(1H,m), 3.90-
4.50(6H,m), 4.63-4.78(1H,br), 7.04(1H,td,J=9.4,2.4Hz),
7.07-7.13(1H,br), 7.37-7.44(1H,m), 8.16-8.49(2H,m), 11.30-
11.70(1H,br), 11.72-11.80(1H,br).

MS (FAB) m/z: 529(M+H⁺).

[Example 145]

N-((3R*,4S*)-1-(3-{tert-butyl(diphenyl)silyl}oxy)-2,2-
dimethylpropanoyl)-4-{[(5-chloroindol-2-yl)carbonyl]-
15 amino}piperidin-3-yl)-5-methyl-4,5,6,7-tetrahydro-
thiazolo[5,4-c]pyridine-2-carboxamide:



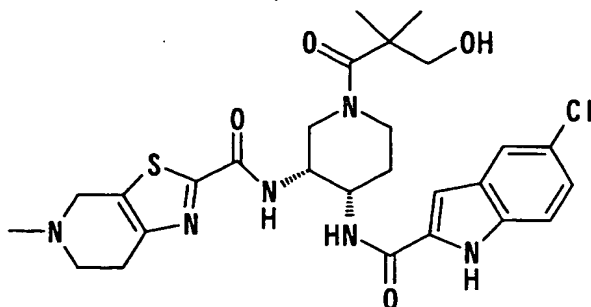
Thionyl chloride (3.0 ml) and a catalytic amount of dimethylformamide were added to a solution of the compound (261 mg) obtained in Referential Example 158 in chloroform (10 ml), and the mixture was stirred overnight at 60°C. The reaction mixture was concentrated under reduced pressure, giving a pale yellow oil. The title compound was obtained from this product and the compound (200 mg) obtained in Example 118 in a similar manner to Example 100.

Melting point: 153°C.

¹H-NMR (CDCl₃) δ: 1.07 (9H, s), 1.39 (6H, d, J=3.9Hz), 1.57 (1H, br. s), 2.26 (1H, d, J=10.7Hz), 2.57 (3H, s), 2.86 (4H, s), 2.97-3.01 (2H, m), 3.78 (4H, s), 4.20 (1H, br. s), 4.33 (1H, d, J=13Hz), 4.42 (1H, br. s), 4.67 (1H, d, J=13Hz), 6.88 (1H, s), 7.20-7.23 (1H, m), 7.32-7.46 (7H, m), 7.64-7.65 (6H, m), 7.86 (1H, d, J=6.8Hz), 8.23 (1H, s), 9.10 (1H, s).

[Example 146]

N-[(3R*, 4S*)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-(3-hydroxy-2,2-dimethylpropanoyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



Tetrabutylammonium fluoride (1 M tetrahydrofuran solution, 0.594 ml) was added to a solution of the compound (241 mg) obtained in Example 145 in
 5 tetrahydrofuran (30 ml) under ice cooling, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and the resultant residue was dissolved in methylene chloride. The solution was washed with water and saturated aqueous
 10 solution of sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:methanol = 9:1) to obtain the title
 15 compound (116 mg).

Melting point: 220°C (decomposed).

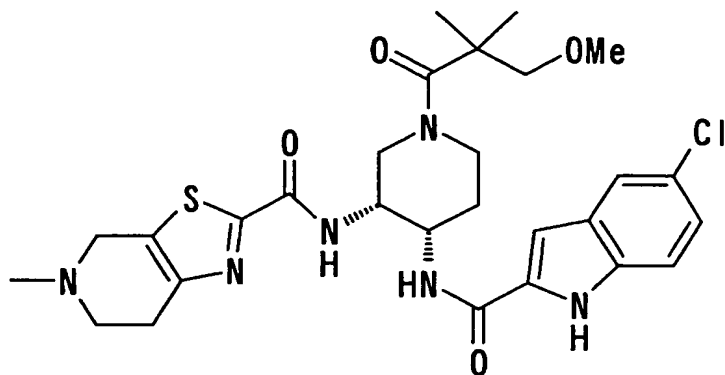
¹H-NMR (DMSO-d₆) δ: 1.17(6H,d,J=8.3Hz), 1.79(1H,br.s),
 1.91-1.97(1H,m), 2.49(3H,s), 2.87(4H,s), 3.35-3.50(4H,m),
 3.81(1H,br.s), 3.97(1H,m), 4.10-4.15(1H,m), 4.32(1H,br.s),
 20 4.42(1H,br.s), 4.52(1H,t,J=5.7Hz), 7.10(1H,s), 7.16-
 7.19(1H,m), 7.42(1H,d,J=8.8Hz), 7.69(1H,s),

8.11 (1H, d, J=8.8Hz), 8.37 (1H, d, J=7.3Hz), 11.8 (1H, s).

MS (FAB) m/z: 573 (M+H⁺).

[Example 147]

N-[(3R*, 4S*)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-(3-methoxy-2,2-dimethylpropanoyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



The title compound was obtained from the compound obtained in Example 118 and the compound obtained in Referential Example 160 in a similar manner to Example 145. Melting point: 240°C (decomposed).

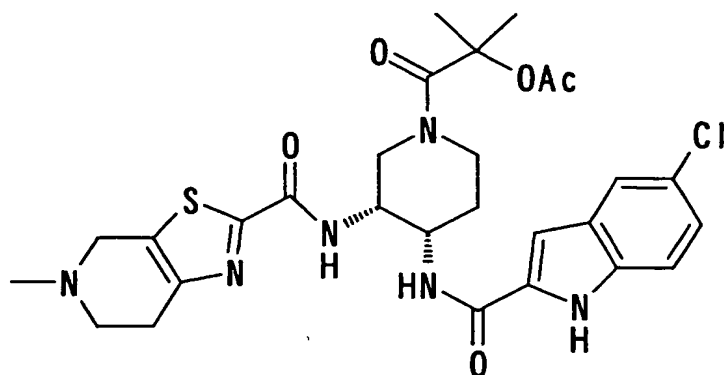
¹H-NMR (CDCl₃) δ: 1.34 (3H, s), 1.37 (3H, s), 1.65-1.77 (1H, m), 2.33-2.37 (1H, m), 2.53 (3H, s), 2.82-3.29 (6H, m), 3.34 (3H, s), 3.41 (1H, d, J=9.3Hz), 3.56 (1H, d, J=9.3Hz), 3.76 (2H, d, J=5.9Hz), 4.26 (1H, m), 4.44-4.53 (2H, m), 4.82 (1H, d, J=13.7Hz), 6.88 (1H, d, J=1.5Hz), 7.20-7.23 (1H, m), 7.33 (1H, d, J=8.8Hz), 7.64 (1H, d, J=1.5Hz), 7.90 (1H, d, J=7.1Hz), 8.22 (1H, d, J=5.1Hz), 9.18 (1H, s).

MS (FAB) m/z: 587 (M+H⁺).

[Example 148]

2-[(3R*, 4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-3-

{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}piperidin-1-yl)-1,1-dimethyl-2-oxoethyl acetate:



5 The title compound was obtained from the compound obtained in Example 118 and 2-acetoxyisobutyryl chloride in a similar manner to Example 100.

Melting point: 190°C (decomposed).

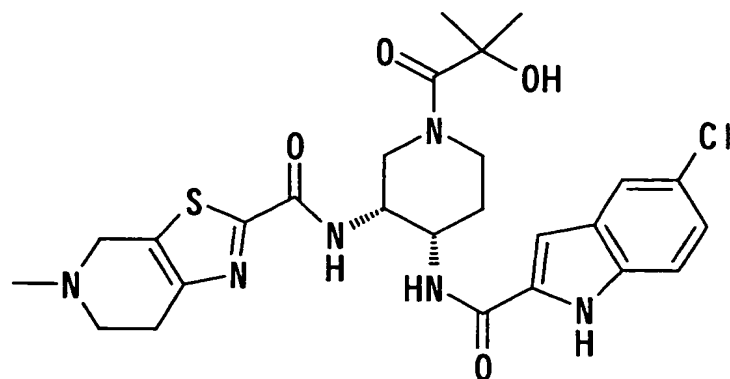
¹H-NMR (CDCl₃) δ: 1.56-1.67(8H,m), 2.08(3H,s),

10 2.35(1H,d,J=10.5Hz), 2.52(3H,s), 2.82-2.84(2H,m), 2.90-2.96(2H,m), 3.14(1H,br.s), 3.75(2H,s), 4.25(1H,br.s), 4.40-4.47(1H,m), 4.54(1H,br.s), 4.80(1H,br.s), 6.86(1H,s), 7.20-7.33(3H,m), 7.64(1H,d,J=1.7Hz), 7.76(1H,d,J=7.3Hz), 9.11(1H,s).

15 MS (FAB) m/z: 601(M+H⁺).

[Example 149]

N-[(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(2-hydroxy-2-methylpropanoyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



Sodium methoxide (76.8 mg) was added to a solution of the compound (190 mg) obtained in Example 148 in methanol (50 ml), and the mixture was stirred overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, the resultant residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:methanol = 9:1) to obtain the title compound (130 mg).

10 Melting point: 190°C (decomposed).

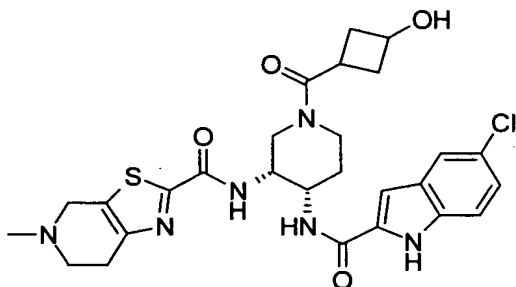
¹H-NMR (CDCl₃) δ: 1.53 (3H, s), 1.56-1.78 (5H, m), 2.34 (1H, d, J=10.5Hz), 2.53 (3H, s), 2.83-2.86 (2H, m), 2.91-2.93 (2H, m), 3.30 (1H, d, J=12.5Hz), 3.75 (2H, s), 4.28 (1H, d, J=5.6Hz), 4.43 (1H, s), 4.65 (1H, d, J=13.5Hz), 4.95 (1H, d, J=13.5Hz), 6.92 (1H, d, J=1.5Hz), 7.20-7.23 (1H, m), 7.33 (1H, d, J=8.6Hz), 7.65 (1H, d, J=2.0Hz), 8.43 (1H, d, J=5.6Hz), 9.14 (1H, s).

MS (FAB) m/z: 559 (M+H⁺).

[Example 150]

20 N-{(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-[(3-hydroxycyclobutyl)carbonyl]piperidin-3-yl}-5-methyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (306 mg) obtained in Example 118, n-
5 methyldmorpholine (200 μ l), 1-hydroxybenzotriazole monohydrate (87 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (197 mg) were added to a solution of the compound (117 mg) obtained Referential Example 152 in a mixed solvent of tetrahydrofuran (20 ml),
10 methylene chloride (3.0 ml) and N,N-dimethylformamide (2.0 ml), and the mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with methylene chloride, and a saturated aqueous solution of sodium hydrogencarbonate was added to separate the mixture into
15 two layers. The resultant organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resultant residue was purified by column chromatography on silica gel (methylene
20 chloride:methanol = 10:1) to obtain a free base (207 mg) of the title compound. The free base was treated with a 1N ethanol solution of hydrochloric acid to obtain the title compound.

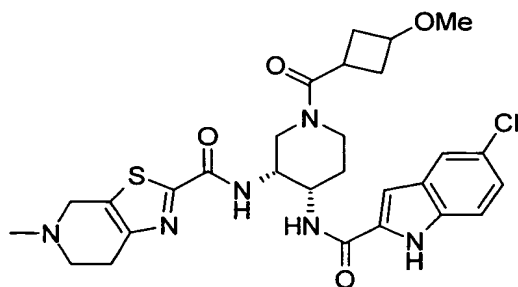
Melting point: 200°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.78-2.10 (4H, m), 2.24-2.68 (3H, m), 2.75-5.20 (14H, m), 2.91 (3H, s), 7.08 (0.5H, s), 7.09 (0.5H, s), 7.18 (1H, dd, J=8.8, 2.0 Hz), 7.42 (1H, d, J=8.8 Hz), 7.70 (1H, d, J=2.0 Hz), 8.05-8.28 (1H, br), 8.38 (0.5H, br. d, J=7.3 Hz), 8.43 (0.5H, br. d, J=8.3 Hz), 10.80-11.25 (1H, br), 11.84 (1H, br. s).

MS (ESI) m/z: 571 (M+H⁺).

[Example 151]

10 N-{(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-[(methoxycyclobutyl)carbonyl]piperidin-3-yl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



15 The title compound was obtained from the compound obtained in Example 118 and the compound obtained in Referential Example 154 in a similar manner to Example 150. Melting point: 191°C (decomposed).

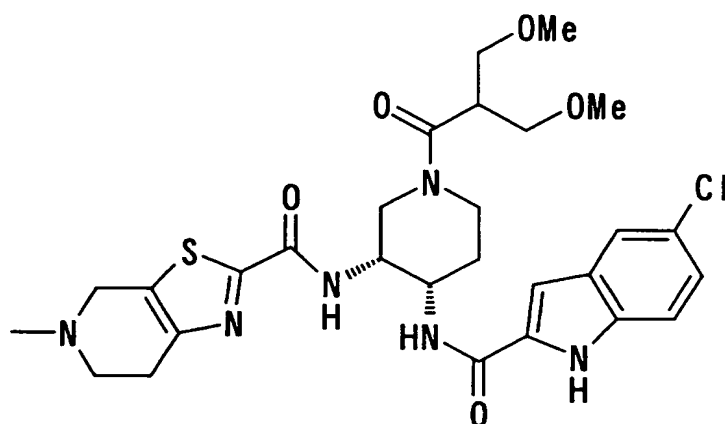
¹H-NMR (DMSO-d₆) δ: 1.69-2.23 (4H, m), 2.25-2.40 (1H, m), 2.71-2.84 (0.5H, m), 2.89-3.93 (9.5H, m), 2.91 (3H, s), 3.01 (1H, s), 3.14 (2H, s), 4.05-4.80 (5H, m), 7.09 (1H, s), 7.18 (1H, d, J=8.4 Hz), 7.42 (1H, d, J=8.4 Hz), 7.70 (1H, s), 8.00-8.30 (1H, br), 8.36-8.53 (1H, m), 11.25-11.75 (1H, br),

11.85(1H,br.s).

MS (ESI) m/z: 585(M+H⁺).

[Example 152]

N-((3R*,4S*)-4-(((5-chloroindol-2-yl)carbonyl)amino)-1-[3-methoxy-2-(methoxymethyl)propanoyl]piperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained by condensing a
10 carboxylic acid obtained by hydrolysis of the compound
obtained in Referential Example 155 with the compound
obtained in Example 118 in a similar manner to Example 150.

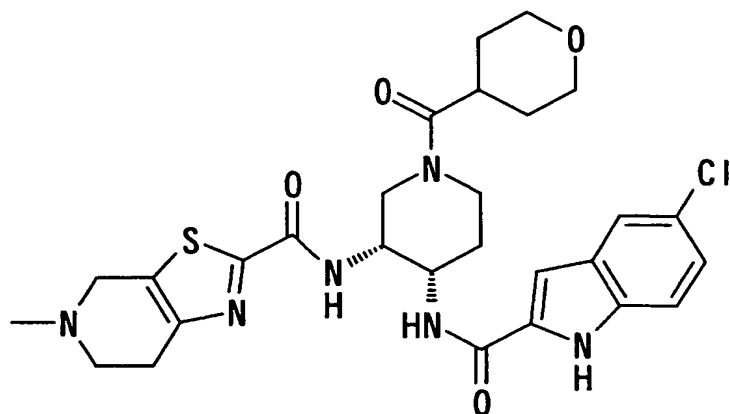
Melting point: 178-184°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.69-1.82(1H,m), 1.84-2.04(1H,m),
15 2.91(3H,s), 3.00-3.75(17H,m), 3.95-4.55(5H,m), 4.60-
4.80(1H,m), 7.10(1H,br.s), 7.18(1H,dd,J=8.8,2.0Hz),
7.42(1H,d,J=8.8Hz), 7.69(0.5H,br.s), 7.71(1H,br.s), 8.18-
8.28(1H,br), 8.35-8.50(1H,br), 11.83(1H,br.s).

MS (ESI) m/z: 603(M+H⁺).

20 [Example 153]

N-[(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-(tetrahydro-2H-pyran-4-ylcarbonyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



5

The title compound was obtained from the compound obtained in Example 118 and the compound obtained in Referential Example 156 in a similar manner to Example 150. Melting point: 225-248°C (decomposed).

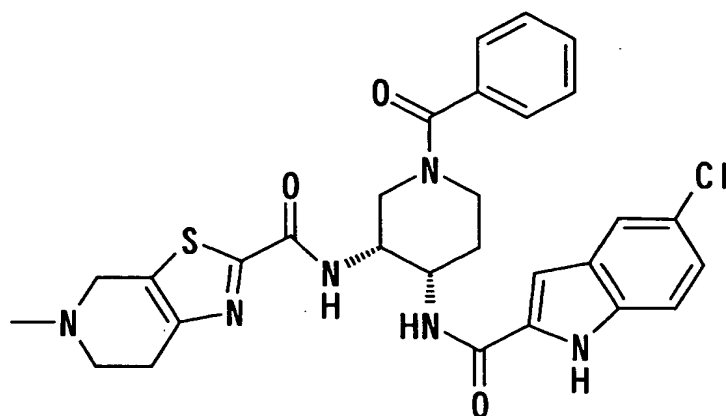
10 ¹H-NMR (DMSO-d₆) δ: 1.55-1.68 (4H,m), 1.70-1.85 (1H,m), 1.85-2.05 (1H,m), 2.60-2.95 (1H,m), 2.89 (3H,s), 2.95-3.20 (3H,m), 3.20-4.00 (9H,m), 4.00-4.80 (4H,m), 7.08 (1H,s), 7.17 (1H,dd,J=8.8,2.0Hz), 7.42 (1H,d,J=8.8Hz), 7.71 (1H,s), 8.00-8.30 (1H,m), 8.35-8.50 (1H,m), 11.16 (1H,br.s),
15 11.85 (1H,s).

MS (ESI) m/z: 585 (M+H⁺).

[Example 154]

N-((3R*,4S*)-1-benzoyl-4-{[(5-Chloroindol-2-yl)carbonyl]amino}piperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
20

hydrochloride:



The title compound was obtained from the compound
obtained in Example 118 and benzoyl chloride in a similar
5 manner to Example 100.

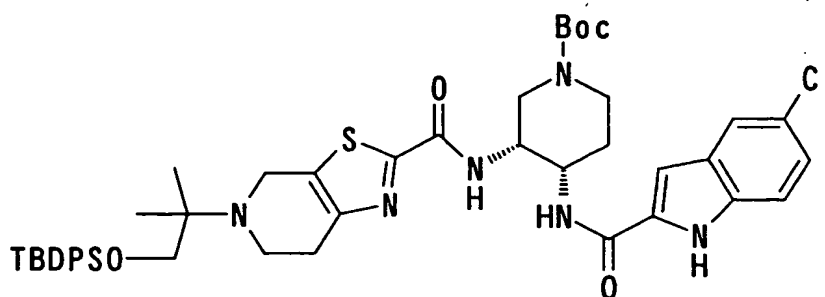
Melting point: 215-225°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.75-1.90 (1H,m), 1.90-2.20 (1H,m),
2.93 (3H,s), 3.10-4.00 (8H,m), 4.05-4.80 (4H,m), 7.00-
7.60 (5H,m), 7.08 (1H,s), 7.16 (1H,dd,J=8.8,1.6Hz),
10 7.40 (1H,d,J=8.8Hz), 7.71 (1H,d,J=1.6Hz), 8.31 (1H,br.s),
8.46 (1H,br.s), 11.39 (1H,br.s), 11.86 (1H,s).

MS (FAB) m/z: 577 (M+H⁺).

[Example 155]

tert-Butyl (3R*,4S*)-3-({[5-(2-{[tert-butyl(diphenyl)-
15 silyl]oxy}-1,1-dimethylethyl)-4,5,6,7-tetrahydrothiazolo-
[5,4-c]pyridin-2-yl]carbonyl}amino)-4-{[(5-chloroindol-2-
yl)carbonyl]amino}piperidine-1-carboxylate:

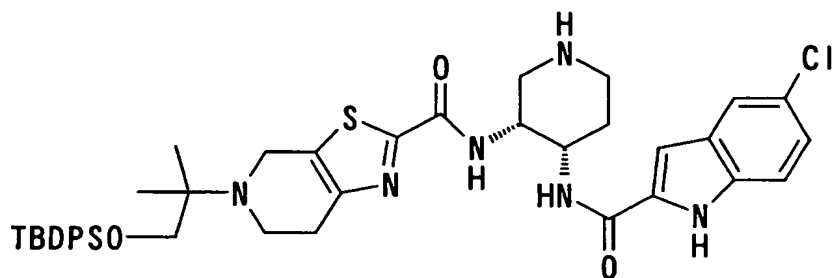


The title compound was obtained from the compound obtained in Referential Example 207 and the compound obtained in Referential Example 42 in a similar manner to Example 91.

¹H-NMR (DMSO-d₆) δ: 1.00 (9H, s), 1.12 (6H, s), 1.15-1.50 (9H, m), 1.63-1.75 (1H, m), 1.82-2.00 (1H, m), 2.60-2.80 (3H, m), 2.83-2.95 (2H, m), 3.12-3.30 (1H, m), 3.30 (2H, s), 3.58 (2H, s), 3.85-4.10 (2H, m), 4.19 (1H, br. s), 4.37 (1H, br. s), 7.04 (1H, s), 7.16 (1H, d, J=9.0Hz), 7.30-7.50 (7H, m), 7.50-7.65 (4H, m), 7.70 (1H, s), 7.99 (1H, d, J=6.8Hz), 8.45 (1H, br. s), 11.82 (1H, s). MS (ESI) m/z: 869 (M+H)⁺

[Example 156]

5-(2-{{tert-Butyl(diphenyl)silyl}oxy}-1,1-dimethylethyl)-N-((3R*,4S*)-4-{{(5-chloroindol-2-yl)carbonyl}amino}-piperidin-3-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide dihydrochloride:



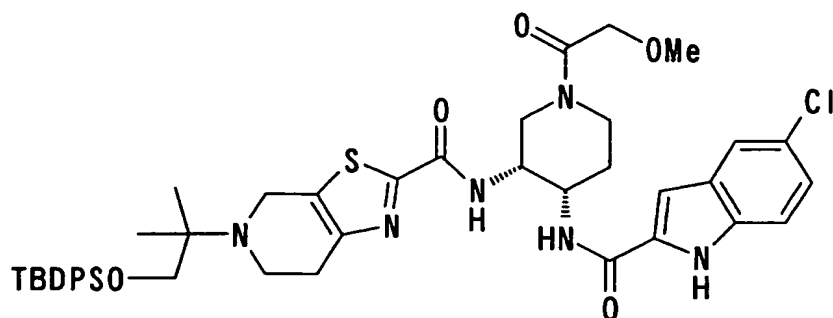
The title compound was obtained by treating the compound obtained in Example 155 in a similar manner to Example 95.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.04 (9H, s), 1.43, 1.48 (total 6H, each s), 1.85-2.00 (1H, m), 2.05-2.20 (1H, m), 2.95-3.20 (2H, m), 3.25-3.60 (6H, m), 3.80-3.90 (1H, m), 3.95-4.05 (1H, m), 4.45-4.55 (1H, m), 4.60-4.85 (3H, m), 7.10-7.20 (2H, m), 7.35-7.55 (7H, m), 7.55-7.75 (5H, m), 8.52 (1H, dd, $J=14.4, 7.8\text{Hz}$),
10 8.93 (1H, br), 9.20-9.40 (2H, m), 11.30-11.50 (1H, m), 11.87, 11.92 (total 1H, each s).

MS (ESI) m/z : 769 ($\text{M}+\text{H}^+$).

[Example 157]

5-(2-{[tert-Butyl (diphenyl)silyl]oxy}-1,1-dimethylethyl)-
15 N-[(3R*, 4S*)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl]-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide:



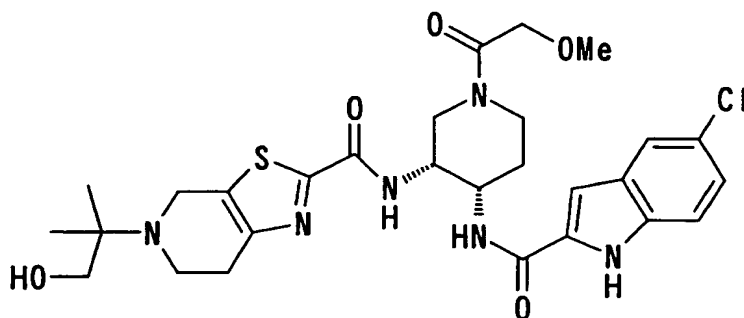
The title compound was obtained from the compound obtained in Example 156 and methoxyacetyl chloride in a similar manner to Example 100.

- 5 $^1\text{H-NMR}$ (CDCl_3) δ : 1.07 (9H, s), 1.20 (6H, s), 1.60-1.85 (1H, m), 2.25-2.40 (1H, m), 2.36 (2H, s), 2.70-3.20 (4H, m), 3.20-3.55 (4H, m), 3.55-3.70 (2H, m), 3.95-4.10 (3H, m), 4.10-4.90 (4H, m), 6.90 (1H, d, $J=1.5\text{Hz}$), 7.15-7.30 (2H, m), 7.30-7.50 (6H, m), 7.60-7.70 (5H, m), 8.15-8.22 (1H, m),
- 10 8.46 (1H, d, $J=5.1\text{Hz}$), 9.28 (1H, s).

MS (ESI) m/z : 842 ($\text{M}+\text{H}^+$).

[Example 158]

- N-[(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl]-5-(2-hydroxy-1,1-
- 15 dimethylethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 157 in a similar manner to Example 146.

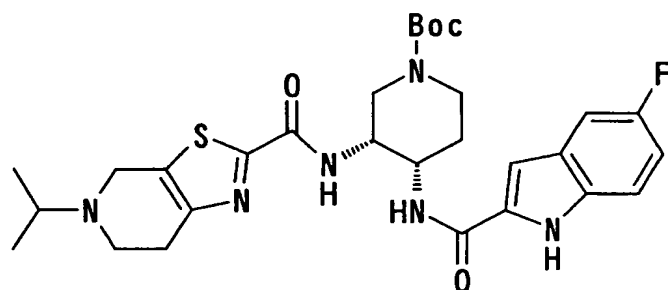
Melting point: 221-232°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.32(3H,s), 1.40(3H,s), 1.70-1.85(1H,m),
5 1.85-2.10(1H,m), 2.60-3.35(8H,m), 3.40-3.82(3H,m), 3.85-
4.05(3H,m), 4.05-4.35(2H,m), 4.50-4.60(1H,m), 4.55-
4.80(2H,m), 5.75-5.85(1H,m), 7.08(1H,br.s),
7.17(1H,d,J=8.8Hz), 7.41(1H,d,J=8.8Hz), 7.71(1H,s), 8.20-
8.35(1H,m), 8.40-8.55(1H,m), 10.00-10.35(1H,m),
10 11.87(1H,s).

MS (ESI) m/z: 603(M+H⁺).

[Example 159]

tert-Butyl (3R*,4S*)-4-{[(5-fluoroindol-2-yl)carbonyl]-
amino}-3-{[(5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
15 pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate:



The title compound was obtained from the compound obtained in Referential Example 209 and the compound obtained in Referential Example 148 in a similar manner to
20 Example 91.

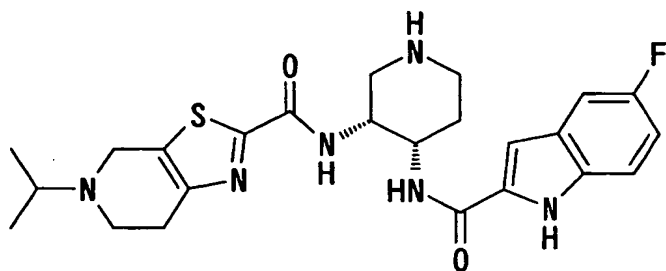
¹H-NMR (CDCl₃) δ: 1.16(6H,d,J=6.6Hz), 1.53(9H,s), 1.65-
1.80(1H,m), 2.23-2.32(1H,m), 2.80-3.10(6H,m), 3.10-

3.25(1H,m), 3.80-3.90(2H,m), 4.00-4.50(4H,m),
6.91(1H,s), 6.95-7.05(1H,m), 7.25-7.40(2H,m), 7.74(1H,br.s),
8.21(1H,br.s), 9.30(1H,s).

MS (ESI) m/z: 585(M+H⁺).

5 [Example 160]

N-((3R*,4S*)-4-{[(5-Fluoroindol-2-yl)carbonyl]amino}-
piperidin-3-yl)-5-isopropyl-4,5,6,7-tetrahydrothiazolo-
[5,4-c]pyridine-2-carboxamide dihydrochloride:



10 The title compound was obtained by treating the
compound obtained in Example 159 in a similar manner to
Example 95.

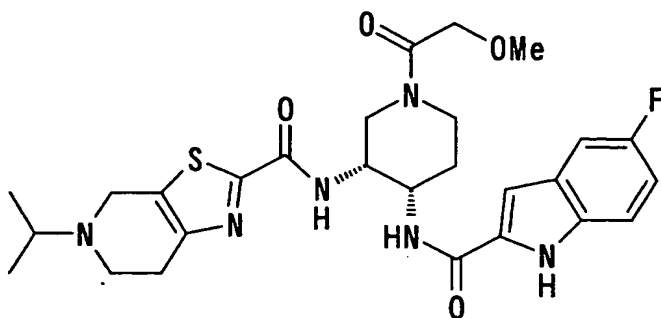
¹H-NMR (DMSO-d₆) δ: 1.28-1.40(6H,m), 1.85-2.00(1H,m), 2.05-
2.20(1H,m), 2.40-2.60(1H,m), 2.95-3.90(8H,m), 4.40-
15 4.55(2H,m), 4.60-4.75(2H,m), 7.00-7.20(2H,m), 7.30-
7.50(2H,m), 8.45-8.60(1H,m), 8.85-9.05(1H,m), 9.05-
9.50(2H,m), 11.60-11.90(2H,m).

MS (ESI) m/z: 485(M+H⁺).

[Example 161]

20 N-[(3R*,4S*)-4-{[(5-Fluoroindol-2-yl)carbonyl]amino}-1-(2-
methoxyacetyl)piperidin-3-yl]-5-isopropyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide

hydrochloride:



The title compound was obtained from the compound
obtained in Example 160 and methoxyacetyl chloride in a
5 similar manner to Example 100.

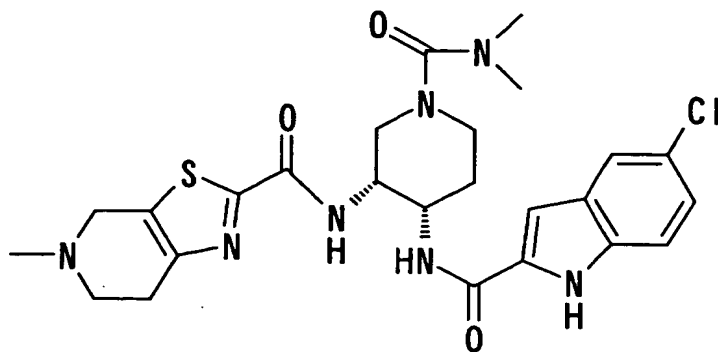
Melting point: 214-228°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.25-1.40 (6H,m), 1.68-1.82 (1H,m), 1.85-
2.10 (1H,m), 2.90-3.60 (8H,m), 3.60-3.85 (2H,m), 3.85-
4.40 (5H,m), 4.40-4.55 (2H,m), 4.60-4.75 (1H,m), 7.00-
10 7.15 (2H,m), 7.35-7.50 (2H,m), 8.15-8.50 (2H,m), 10.80-
11.30 (1H,m), 11.73 (1H,d,J=6.6Hz).

MS (ESI) m/z: 557 (M+H⁺).

[Example 162]

N-((3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-
15 [(dimethylamino)carbonyl]piperidin-3-yl)-5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and N,N-dimethylcarbamoyl chloride in a similar manner to Example 100.

5 Melting point: 267-270°C (decomposed).

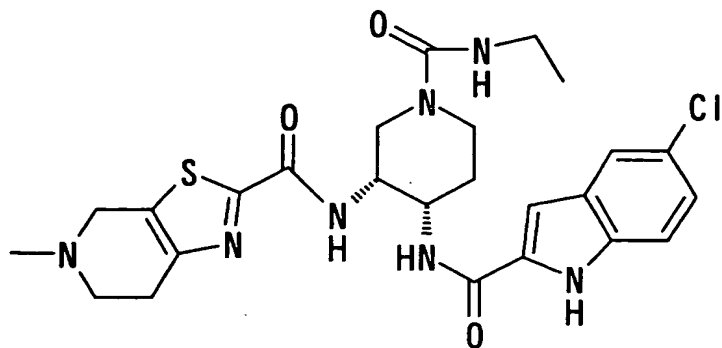
¹H-NMR (DMSO-d₆) δ: 1.65-1.78 (1H,m), 1.97-2.10 (1H,m),
2.70 (6H,s), 2.90 (3H,s), 2.95-3.80 (8H,m), 4.25-4.80 (4H,m),
7.08 (1H,s), 7.16 (1H,dd,J=8.8,1.8Hz), 7.41 (1H,d,J=8.8Hz),
7.70 (1H,s), 8.31 (1H,br.s), 8.40 (1H,d,J=7.3Hz), 11.15-

10 11.60 (1H,m), 11.82 (1H,s).

MS (ESI) m/z: 544 (M+H⁺).

[Example 163]

N-((3R*,4S*)-4-({[(5-chloroindol-2-yl)carbonyl]amino}-1-
[(ethylamino)carbonyl]piperidin-3-yl)-5-methyl-4,5,6,7-
15 tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and ethyl isocyanate in a similar manner to Example 100.

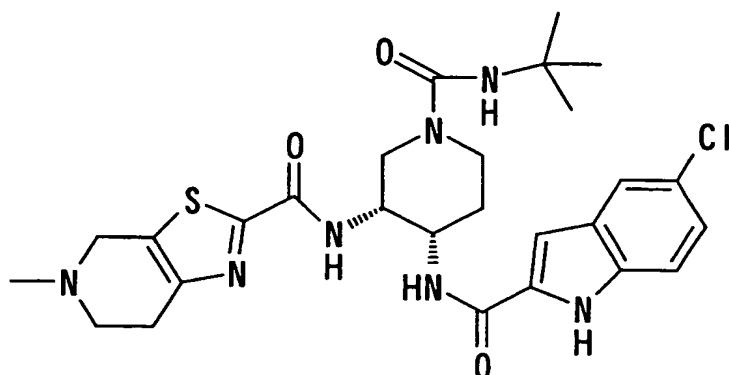
5 Melting point: 221-235°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 0.98 (3H, t, J=7.1Hz), 1.60-1.70 (1H, m),
 1.80-1.95 (1H, m), 2.90 (3H, s), 2.95-3.40 (6H, m), 3.40-
 4.00 (4H, m), 4.25-4.80 (4H, m), 6.60-6.80 (1H, m), 7.09 (1H, s),
 7.16 (1H, dd, J=8.8, 1.9Hz), 7.41 (1H, d, J=8.8Hz),
 10 7.68 (1H, d, J=1.9Hz), 8.02 (1H, br. s), 8.35 (1H, d, J=7.1Hz),
 11.20-11.70 (1H, m), 11.82 (1H, s).

MS (FAB) m/z: 544 (M+H⁺).

[Example 164]

N-((3R*,4S*)-1-[(tert-Butylamino)carbonyl]-4-[[5-
 15 chloroindol-2-yl)carbonyl]amino)piperidin-3-yl)-5-methyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
 hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and tert-butyl isocyanate in a similar manner to Example 100.

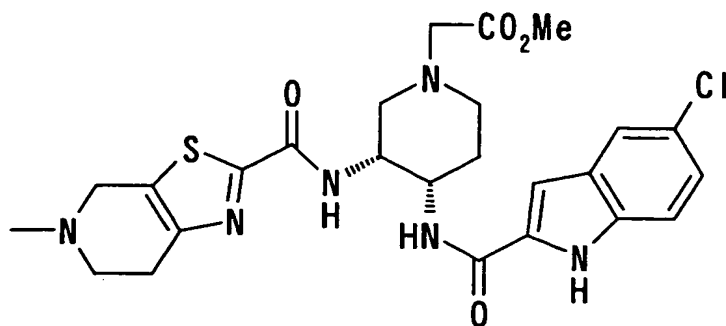
5 Melting point: 236-238°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.21(9H,s), 1.60-1.70(1H,m), 1.80-1.90(1H,m), 2.87(3H,s), 3.00-3.40(6H,m), 3.49(1H,br.s), 3.80-3.90(1H,m), 3.90-4.00(1H,m), 4.20-4.35(2H,m), 4.47(1H,br.s), 5.90(1H,s), 7.06(1H,s), 7.16(1H,dd,J=8.8,1.9Hz), 7.41(1H,d,J=8.8Hz), 7.67(1H,d,J=1.9Hz), 8.04(1H,d,J=6.8Hz), 8.34(1H,d,J=7.3Hz), 11.22(1H,br.s), 11.79(1H,s).

MS (FAB) m/z: 572(M+H⁺).

[Example 165]

15 Methyl 2-((3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino})piperidin-3-yl)acetate dihydrochloride:



The title compound was obtained from the compound obtained in Example 118 and methyl bromoacetate in a similar manner to Example 102.

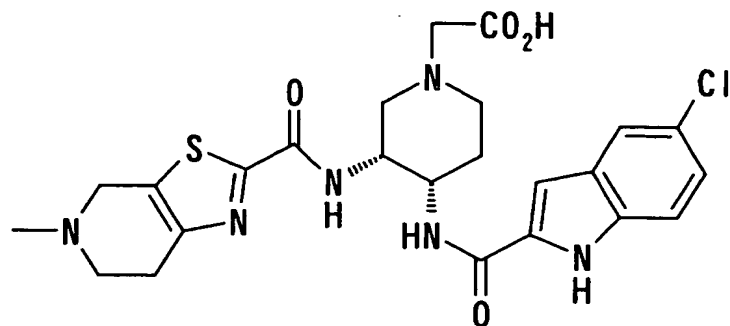
5 Melting point: 253-255°C (decomposed).

¹H-NMR (DMSO-d₆, 80°C) δ: 1.95-2.10 (1H, m), 2.10-2.25 (1H, m), 2.88 (3H, s), 3.00-3.73 (8H, m), 3.75 (3H, s), 3.97-4.15 (2H, m), 4.30-4.80 (4H, m), 7.08-7.20 (2H, m), 7.44 (1H, d, J=8.6 Hz), 7.63 (1H, d, J=2.0 Hz), 8.42 (1H, d, J=7.3 Hz), 8.62 (1H, br. s), 11.82 (1H, br. s).

MS (ESI) m/z: 545 (M+H⁺).

[Example 166]

2-((3R*,4S*)-4-(((5-Chloroindol-2-yl)carbonyl)amino)-3-
 {[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-
 15 yl)carbonyl]amino}piperidin-3-yl)acetic acid
 hydrochloride:



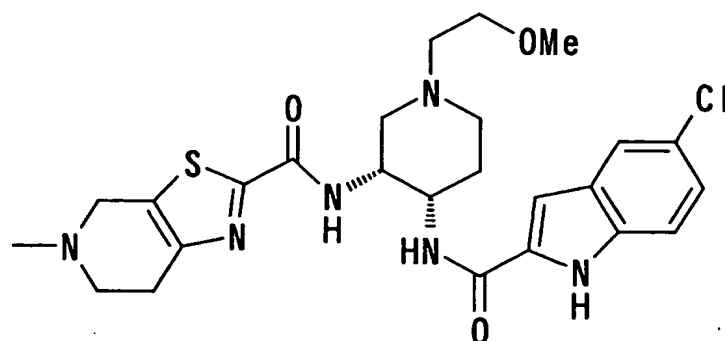
The title compound was obtained by treating the compound obtained in Example 165 in a similar manner to Example 101.

5 Melting point: 234-240°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.75-1.95(1H,m), 2.05-2.20(1H,m),
 2.88(3H,s), 2.95-3.90(10H,m), 4.20-4.70(4H,m), 7.11(1H,s),
 7.16(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz),
 7.66(1H,d,J=2.0Hz), 8.46(1H,br.d,J=7.8Hz), 8.65(1H,br.s),
 10 11.60-12.70(2H,br.s), 11.91(1H,br.s).

[Example 167]

N-[(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(2-methoxyethyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide dihydrochloride:



The title compound was obtained from the compound obtained in Example 118 and 2-bromoethyl methyl ether in a similar manner to Example 102 (NMR was measured in the form of a free base).

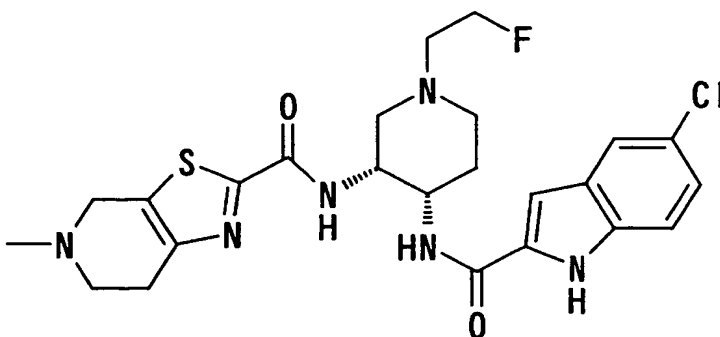
5 Melting point: 238-242°C (decomposed).

¹H-NMR (CDCl₃) δ: 1.75-1.83(2H,m), 2.27-2.39(2H,m), 2.52(3H,s), 2.60-2.66(1H,m), 2.69-2.75(1H,m), 2.81-2.90(2H,m), 2.96-3.07(2H,m), 3.41(3H,s), 3.53-3.60(2H,m), 3.75(each 1H,AB type d,J=15.5Hz), 4.02-4.05(1H,m), 10 4.40(1H,br), 6.88(1H,d,J=1.5Hz), 7.18-7.21(1H,m), 7.31-7.33(1H,m), 7.63(1H,d,J=1.5Hz), 8.17(1H,d,J=5.0Hz), 8.26(1H,d,J=7.0Hz), 9.30(1H,br.s).

MS (FAB) m/z: 531(M+H⁺).

[Example 168]

15 N-[(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(2-fluoroethyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide dihydrochloride:



The title compound was obtained from the compound obtained in Example 118 and 2-fluoroethyl bromide in a similar manner to Example 102 (NMR was measured in the

form of a free base).

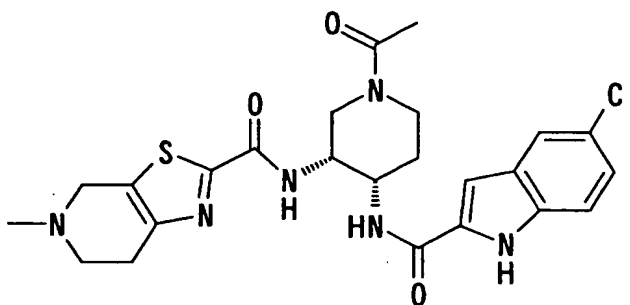
Melting point: 228-233°C (decomposed).

¹H-NMR (CDCl₃) δ: 1.77(2H,dq,J=12.5,4.0Hz), 2.28-2.32(1H,m),
2.41(1H,t,J=12.5Hz), 2.52(3H,s), 2.65(1H,d,J=10.5Hz),
5 2.76-2.81(1H,m), 2.83-2.86(3H,m), 2.98-3.05(3H,m),
3.75(each 1H,AB type d,J=15.5Hz), 4.02-4.08(1H,m),
4.45(1H,br), 4.54-4.59(1H,m), 4.64-4.70(1H,m),
6.87(1H,d,J=1.5Hz), 7.19-7.22(1H,m), 7.32(1H,d,J=8.5Hz),
7.64(1H,d,J=2.0Hz), 8.11(1H,d,J=5.5Hz), 8.20(1H,d,J=7.3Hz),
10 9.30(1H,br).

MS (FAB) m/z: 519(M+H⁺).

[Example 169]

N-((3R,4S)-1-Acetyl-4-[[(5-chloroindol-2-yl)carbonyl]-
amino]piperidin-3-yl)-5-methyl-4,5,6,7-tetrahydro-
15 thiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



A 4N dioxane solution (7.0 ml) of hydrochloric acid
was added to a dioxane solution (15 ml) of the compound
(630 mg) obtained in Referential Example 214, and the
20 mixture was stirred at room temperature for 1 hour. The
reaction mixture was concentrated under reduced pressure.

The thus-obtained yellow solids (590 mg) and the compound (379 mg) obtained in Referential Example 10 were used to obtain a free base (330 mg) of the title compound in a similar manner to Example 91. This free base was treated with an ethanol solution of hydrochloric acid to obtain the title compound (NMR was measured in the form of a free base).

Melting point: 202-222°C (decomposed).

¹H-NMR (DMSO-d₆) δ: 1.65-1.85(1H,m),

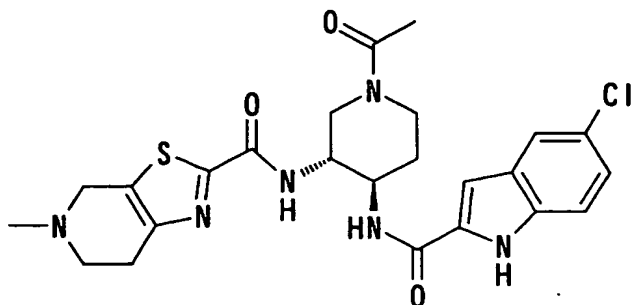
1.87,2.06(total 3H,each s), 1.88-2.10(1H,m), 2.37(3H,s),
2.65-2.77(2H,m), 2.79-2.89(2H,m), 2.99-3.09(0.5H,m), 3.30-
3.52(2H,m), 3.64(2H,s), 3.70-3.80(0.5H,m), 3.96-4.21(2H,m),
4.27(1H,br.s), 4.35-4.48(1H,m), 7.07,7.11(total 1H,each s),
7.18(1H,d,J=8.8Hz), 7.42(1H,d,J=8.8Hz), 7.71(1H,s), 8.16-
8.22(1H,m), 8.37,8.46(total 1H,each d,J=7.8Hz),
11.81,11.83(total 1H,each s).

MS (ESI) m/z: 515(M+H⁺).

[α]_D²⁵ = -56.0° (c = 0.50, methanol).

[Example 170]

N-((3R,4R)-1-Acetyl-4-{[(5-chloroindol-2-yl)carbonyl]-
amino}piperidin-3-yl)-5-methyl-4,5,6,7-tetrahydro-
thiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 219 and Referential Example 10 in a similar manner to Example 169.

5 Melting point: 221-238°C.

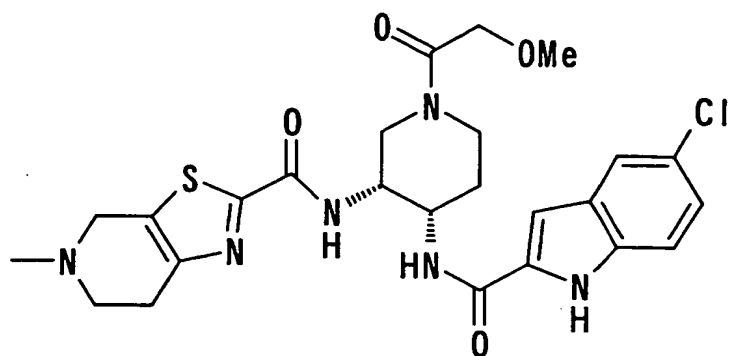
¹H-NMR (DMSO-d₆) δ: 1.45-1.56(0.5H,m), 1.60-1.70(0.5H,m),
1.89-2.01(1H,m), 2.05(3H,s), 2.51-2.67(1H,m), 2.88(3H,s),
3.00-3.22(3H,m), 3.31-3.40(3H,m), 3.56-3.67(0.5H,m), 3.78-
4.02(1.5H,m), 4.22-4.44(2H,m), 4.56-4.72(1H,m), 7.02(1H,s),
10 7.15(1H,dd,J=8.8,2.0Hz), 7.37(1H,d,J=8.8Hz),
7.67(1H,d,J=2.0Hz), 8.42(1H,d,J=9.8Hz), 8.67-8.78(1H,m),
11.02-11.14(1H,m), 11.72(0.5H,s), 11.74(0.5H,s).

MS (FAB) m/z: 515 (M+H⁺).

[α]_D²⁵ = -105.4° (c = 0.58, methanol).

15 [Example 171]

N-[(3R,4S)-4-[[[(5-Chloroindol-2-yl)carbonyl]amino]-1-(2-methoxyacetyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 221 in a similar manner to Example 169.

5 Melting point: 207–220°C (decomposed).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.70–1.80 (1H,m), 1.85–2.05 (1H,m),
2.90 (3H,s), 3.00–3.20 (2H,m), 3.16 (3H,s), 3.22–3.82 (7H,m),
3.88–4.80 (5H,m), 7.09 (1H,d,J=9.0Hz),
7.17 (1H,dd,J=8.8,1.9Hz), 7.42 (1H,d,J=8.8Hz),

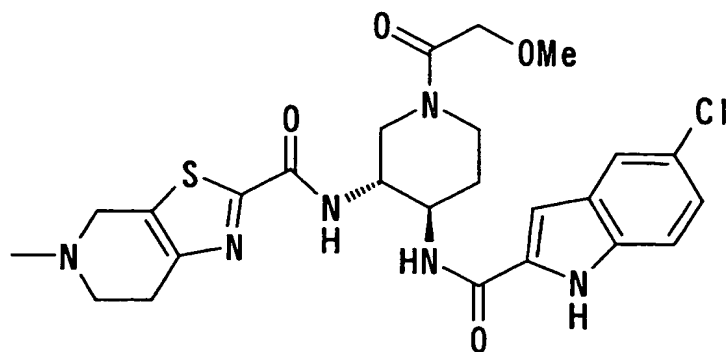
10 7.70 (1H,d,J=1.9Hz), 8.29 (1H,br.s), 8.40–8.50 (1H,m), 11.20–
11.50 (1H,m), 11.85 (1H,s).

MS (ESI) m/z : 545 ($\text{M}+\text{H}^+$).

$[\alpha]^{25}_{\text{D}} = -53.4^\circ$ ($c = 0.52$, methanol).

[Example 172]

15 N-[(3R,4R)-4-{{[(5-chloroindol-2-yl)carbonyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 223 in a similar manner to Example 169.

5 Melting point: 213-230°C.

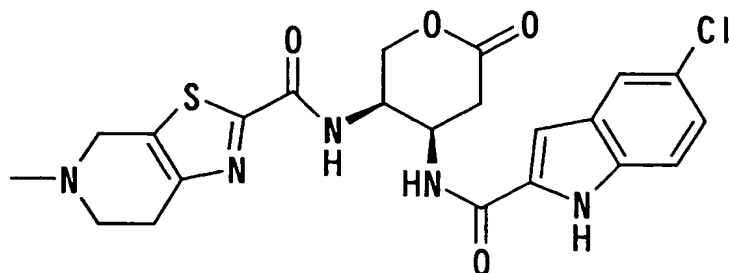
¹H-NMR (DMSO-d₆) δ: 1.45-1.56 (0.5H,m), 1.61-1.70 (0.5H,m), 1.89-2.00 (1H,m), 2.05 (3H,s), 2.45-2.67 (1H,m), 2.88 (3H,s), 3.00-3.21 (4H,m), 3.32-3.56 (7H,m), 3.78-3.89 (2H,m), 4.00-4.24 (2H,m), 4.26-4.43 (2H,m), 7.02 (1H,s), 7.13 (1H,dd,J=8.8,2.0Hz), 7.37 (1H,d,J=8.8Hz), 7.67 (1H,d,J=2.0Hz), 8.41 (1H,d,J=9.8Hz), 8.74 (1H,d,J=9.8Hz), 10.80-10.90 (1H,m), 11.72 (1H,s).

MS (FAB) m/z: 545 (M+H⁺).

[α]²⁵_D = -100.3° (c = 0.51, methanol).

15 [Example 173]

N-((3R,4R)-4-({[5-chloroindol-2-yl]carbonyl}amino)-6-oxotetrahydro-2H-pyran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



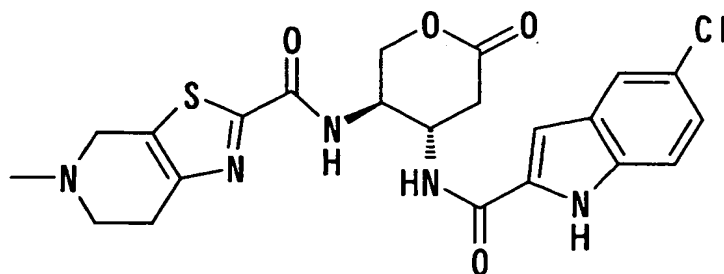
The title compound was obtained from the low-polar compound obtained in Referential Example 176 and the compound obtained in Referential Example 10 in a similar manner to Example 169.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 2.41-2.56(2H,m), 2.91(3H,s), 3.01-3.23(1H,m), 3.24-3.56(5H,m), 3.62-3.67(1H,m), 4.21-4.44(1H,m), 4.56-4.78(2H,m), 7.11(1H,s), 7.16(1H,dd, $J=8.8, 2.0\text{Hz}$), 7.22(1H,d, $J=8.5\text{Hz}$), 7.41(1H,d, $J=8.8\text{Hz}$), 7.69(1H,d, $J=2.0\text{Hz}$), 8.40-8.50(1H,m), 11.34-11.56(1H,m), 11.82(1H,s).

MS (FAB) m/z : 488 ($\text{M}+\text{H}^+$).

[Example 174]

N-((3R,4S)-4-({[(5-chloroindol-2-yl)carbonyl]amino}-6-oxotetrahydro-2H-pyran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



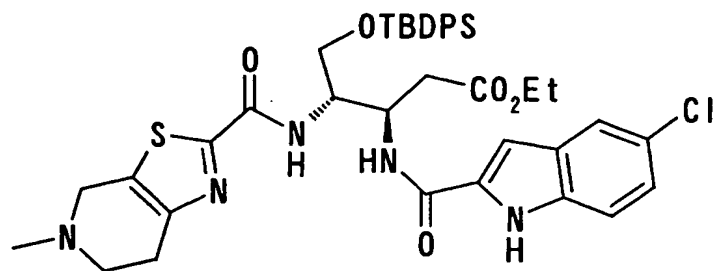
The title compound was obtained from the high-polar compound obtained in Referential Example 176 and the compound obtained in Referential Example 10 in a similar manner to Example 169.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.41-2.56 (2H,m), 2.91 (3H,s), 3.23-3.41 (2H,m), 3.43-3.50 (2H,m), 3.56-3.67 (2H,m), 4.37 (1H,dd, $J=13.9, 7.1\text{Hz}$), 4.40-4.50 (1H,m), 4.56-4.78 (2H,m), 7.12 (1H,s), 7.17 (1H,dd, $J=8.8, 2.0\text{Hz}$), 7.41 (1H,d, $J=8.8\text{Hz}$), 7.71 (1H,d, $J=2.0\text{Hz}$), 8.44 (1H,d, $J=8.5\text{Hz}$), 8.15 (1H,d, $J=8.5\text{Hz}$),
10 11.42-11.53 (1H,m), 11.79 (1H,s).

MS (FAB) m/z : 488 ($\text{M}+\text{H}^+$).

[Example 175]

Ethyl (3R,4S)-5-{[tert-butyl(diphenyl)silyl]oxy}-3-{[(5-chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-
15 valerate:



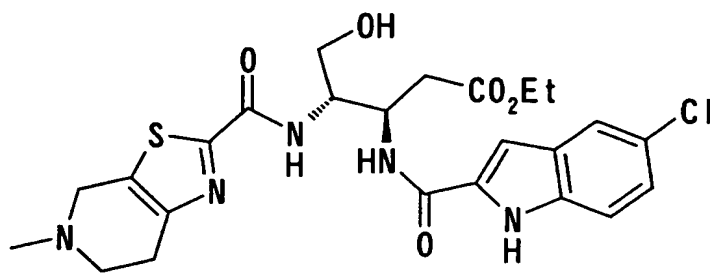
The title compound was obtained from the compound obtained in Referential Example 225 in a similar manner to
20 Example 169.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.09 (9H,s), 1.21 (3H,t, $J=7.4\text{Hz}$), 2.49 (3H,s), 2.65 (1H,dd, $J=15.9, 5.4\text{Hz}$), 2.67-2.90 (5H,m),

3.60 (1H, d, J=14.9Hz), 3.72 (1H, d, J=14.9Hz), 3.78-3.91 (2H, m),
4.00-4.21 (2H, m), 4.43-4.50 (1H, m), 4.78-4.89 (1H, m),
6.81 (1H, s), 7.20 (1H, dd, J=8.8, 2.0Hz), 7.32-7.52 (m, 7H),
7.63-7.74 (6H, m), 7.89-8.01 (1H, m), 9.18 (1H, s).

5 [Example 176]

Ethyl (3R,4S)-3-{[(5-chloroindol-2-yl)carbonyl]amino}-5-hydroxy-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}valerate:



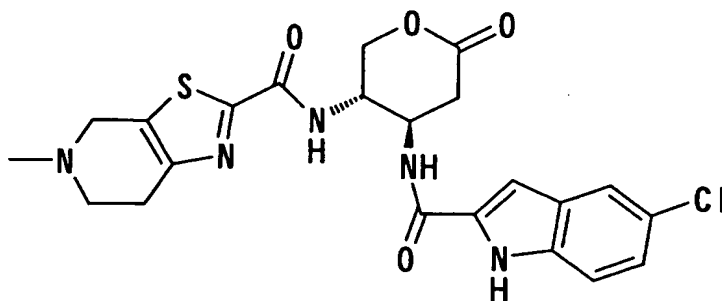
10 After hydrogen fluoride·pyridine (0.4 ml) was added dropwise to a mixture solution composed of the compound (0.54 g) obtained in Example 175, pyridine (4.0 ml) and tetrahydrofuran (10 ml) under ice cooling, the reaction mixture was stirred for 18 hours while the temperature
15 thereof was gradually raised to room temperature. The reaction mixture was concentrated, and the resultant residue was purified by column chromatography on silica gel (chloroform:methanol = 9:1) to obtain the title compound (0.31 g).

20 ¹H-NMR (CDCl₃) δ: 1.20 (3H, t, J=7.4Hz), 2.49 (3H, s), 2.67-2.90 (6H, m), 3.62-3.74 (3H, m), 3.78-3.94 (1H, m), 4.00-4.20 (2H, m), 4.30-4.40 (1H, m), 4.80-4.89 (1H, m), 6.93 (1H, s),

7.23 (1H, dd, J=8.8, 2.0 Hz), 7.33 (1H, d, J=8.8 Hz),
7.56 (1H, d, J=8.5 Hz), 7.61 (1H, d, J=2.0 Hz), 7.88 (1H, d, J=8.5 Hz),
9.29 (1H, s).

[Example 177]

- 5 N-((3S, 4R)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-6-oxotetrahydro-2H-pyran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



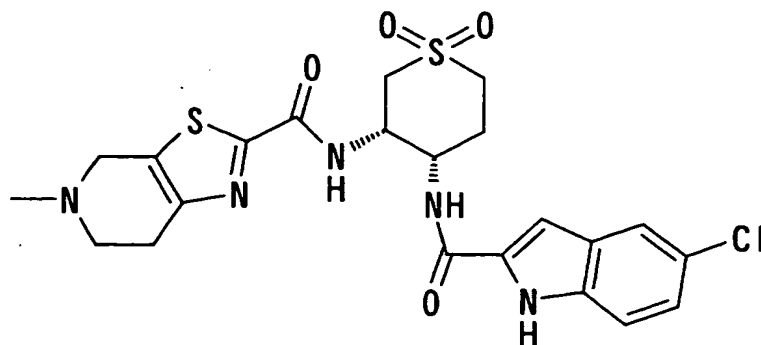
- A 4N dioxane solution (20 ml) of hydrochloric acid
10 was added to the compound (0.31 g) obtained in Example 176, and the mixture was heated under reflux for 4 hours. The reaction mixture was concentrated, and the resultant residue was recrystallized from diethyl ether to obtain the title compound (0.23 g).

- 15 Melting point: 221-238°C (decomposed).

¹H-NMR and MS (FAB): The same as those of the enantiomer in Example 174.

[Example 178]

- N-((3R*, 4R*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1,1-dioxohexahydro-1-thiopyran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
20 hydrochloride:



A free base of the title compound was obtained from the compound obtained in Referential Example 227 and 5-chloroindole-2-carboxylic acid in a similar manner to

5 Example 91. This free base was treated with an ethanol solution of hydrochloric acid to obtain the title compound.

Melting point: 241-244°C.

¹H-NMR (DMSO-d₆) δ: 2.14 (1H, br), 2.30-2.34 (1H, m),

2.92 (3H, s), 3.10-3.18 (2H, m), 3.41 (4H, br), 3.68 (2H, br),

10 4.44 (1H, br), 4.63-4.78 (3H, m), 7.16-7.18 (1H, m), 7.21 (1H, s),

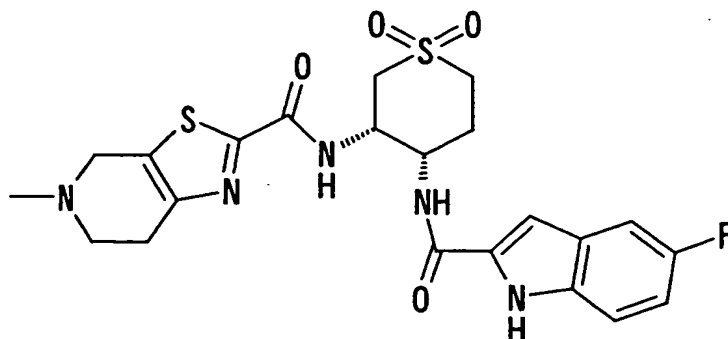
7.43 (1H, d, J=8.5Hz), 7.67 (1H, d, J=4.6Hz), 8.39 (1H, br),

8.94 (1H, br), 11.82 (1H, br).

MS (ESI) m/z: 522 (M+H⁺).

[Example 179]

15 N-((3R*,4R*)-4-{[(5-Fluoroindol-2-yl)carbonyl]amino}-1,1-dioxohexahydro-1-thiopyran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



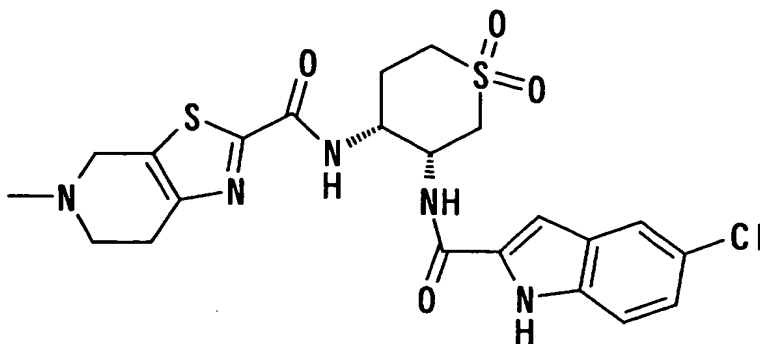
A free base of the title compound was obtained from the compound obtained in Referential Example 227 and 5-fluoroindole-2-carboxylic acid in a similar manner to
 5 Example 91. This free base was treated with an ethanol solution of hydrochloric acid to obtain the title compound. Melting point: 243-245°C.

¹H-NMR (DMSO-d₆) δ: 2.14(1H,br), 2.30-2.33(1H,m),
 2.92(3H,s), 3.13(2H,br), 3.51(4H,br), 3.63(2H,br),
 10 4.63(3H,br), 4.78(1H,br), 7.01-7.05(1H,m), 7.21(1H,s),
 7.37-7.44(2H,m), 8.36(1H,br), 8.93(1H,d,J=6.8Hz),
 11.72(1H,br).

MS (ESI) m/z: 506(M+H⁺).

[Example 180]

15 N-((3R*,4R*)-3-[[(5-Chloroindol-2-yl)carbonyl]amino]-1,1-dioxohexahydro-1-thiopyran-4-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



A free base of the title compound was obtained from the compound obtained in Referential Example 229 and the compound obtained in Referential Example 10 in a similar
 5 manner to Example 91. This free base was treated with an ethanol solution of hydrochloric acid to obtain the title compound.

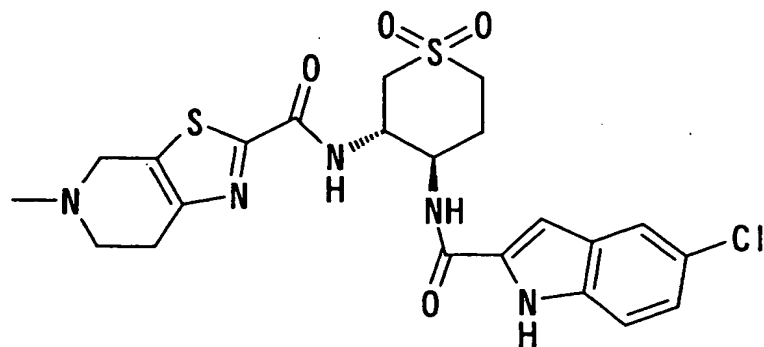
Melting point: 242-247°C.

¹H-NMR (DMSO-d₆) δ: 2.16(1H,br), 2.45(1H,br), 2.93(3H,s),
 10 3.13(2H,br), 3.26(4H,br), 3.69(2H,br), 4.45(1H,br), 4.65-4.77(3H,m), 7.01(1H,s), 7.17(1H,dd,J=8.7,1.4Hz), 7.43(1H,d,J=8.5Hz), 7.69(1H,s), 8.35-8.40(1H,m), 9.04(1H,br), 11.86(1H,s).

MS (ESI) m/z: 522(M+H⁺).

15 [Example 181]

N-((3R*,4S*)-4-(((5-Chloroindol-2-yl)carbonyl)amino)-1,1-dioxohexahydro-1-thiopyran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



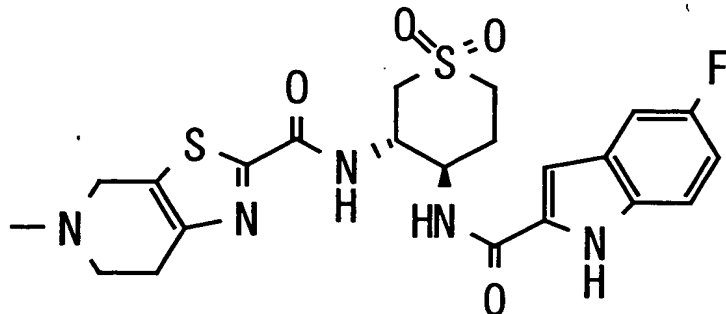
A free base of the title compound was obtained from the compound obtained in Referential Example 231 and 5-chloroindole-2-carboxylic acid in a similar manner to
 5 Example 91. This free base was treated with an ethanol solution of hydrochloric acid to obtain the title compound. Melting point: 244-249°C.

¹H-NMR (DMSO-d₆) δ: 2.17-2.27 (2H,m), 2.90 (3H,s),
 3.09 (1H,br), 3.18-3.21 (2H,m), 3.31-3.34 (2H,m), 3.60-
 10 3.67 (3H,m), 4.41-4.49 (2H,m), 4.54-4.59 (2H,m), 7.04 (1H,s),
 7.09-7.13 (1H,m), 7.39 (1H,d,J=8.5Hz), 7.61 (1H,d,J=9.9Hz),
 8.52-8.56 (1H,m), 8.83-8.85 (1H,m), 11.65 (1H,d,J=11.9Hz).

MS (ESI) m/z: 522 (M+H⁺).

[Example 182]

15 N-((3R*,4S*)-4-{[(5-Fluoroindol-2-yl)carbonyl]amino}-1,1-dioxohexahydro-1-thiopyran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



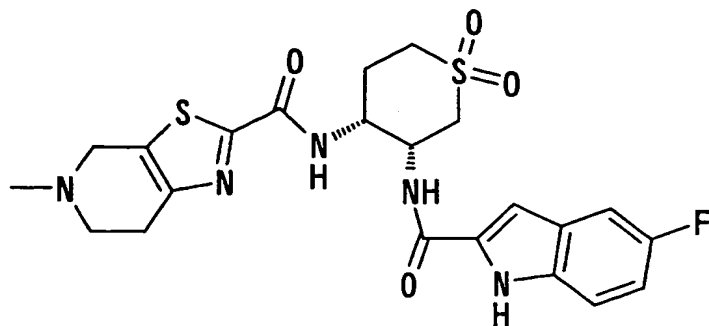
A free base of the title compound was obtained from the compound obtained in Referential Example 231 and 5-fluoroindole-2-carboxylic acid in a similar manner to
 5 Example 91. This free base was treated with an ethanol solution of hydrochloric acid to obtain the title compound. Melting point: 236-241°C.

¹H-NMR (DMSO-d₆) δ: 2.20-2.24 (2H,m), 2.89 (3H,s), 3.07 (1H,br), 3.19-3.22 (2H,m), 3.60-3.66 (4H,m), 4.43-
 10 4.58 (5H,m), 6.95-7.00 (1H,m), 7.04 (1H,s), 7.32-7.38 (2H,m), 8.50 (1H,d,J=8.5Hz), 8.83 (1H,d,J=8.5Hz), 11.59 (1H,s).

MS (ESI) m/z: 506 (M+H⁺).

[Example 183]

N-((3R*,4R*)-3-[[(5-Fluoroindol-2-yl) carbonyl] amino]-1,1-dioxohexahydro-1-thiopyran-4-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
 15 hydrochloride:



A free base of the title compound was obtained from the compound obtained in Referential Example 233 and the compound obtained in Referential Example 10 in a similar manner to Example 91. This free base was treated with an ethanol solution of hydrochloric acid to obtain the title compound.

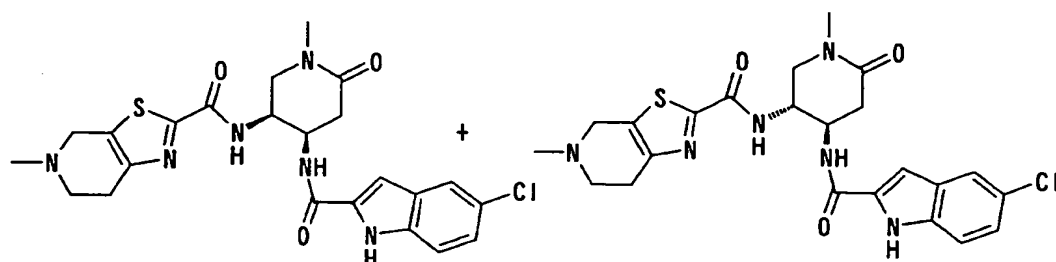
Melting point: 244-249°C.

¹H-NMR (DMSO-d₆) δ: 2.12-2.18 (1H, m), 2.50 (1H, br), 2.92 (3H, s), 3.17 (3H, br), 3.50-3.61 (5H, m), 4.45 (1H, br), 4.62-4.78 (3H, m), 6.98-7.03 (2H, m), 7.36-7.42 (2H, m), 8.30 (1H, br), 9.00 (1H, d, J=8.0Hz), 11.74 (1H, s).

MS (ESI) m/z: 506 (M+H⁺).

[Example 184]

N-((3S,4R)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-methyl-6-oxopiperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (low-polar compound) and N-((3R,4R)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-methyl-6-oxopiperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (high-polar compound):



Low-polar compound

High-polar compound

The title compound was obtained from the compound obtained in Referential Example 236 and the compound obtained in Referential Example 10 in a similar manner to Example 169.

Low-polar compound:

Melting poing: 189-203°C (decomposed).

¹H-NMR (CDCl₃) δ: 2.52 (3H, s), 2.59 (1H, q, J=8.8Hz), 2.71-2.78 (2H, m), 2.89-3.00 (2H, m), 3.03 (3H, s), 3.12 (1H, dd, J=17.6, 5.4Hz), 3.43 (1H, dd, J=12.7, 5.1Hz), 3.70 (1H, d, J=15.2Hz), 3.77 (1H, d, J=15.2Hz), 3.83 (1H, dd, J=12.7, 3.9Hz), 4.55-4.67 (2H, m), 6.99 (1H, s), 7.23 (1H, dd, J=8.8, 2.0Hz), 7.33 (1H, d, J=8.8Hz), 7.65 (1H, d, J=2.0Hz), 8.07 (1H, d, J=5.1Hz), 8.16 (1H, d, J=5.4Hz), 9.43 (1H, s).

MS (FAB) m/z: 501 (M+H⁺).

High-polar compound:

Melting point: 183-195°C (decomposed).

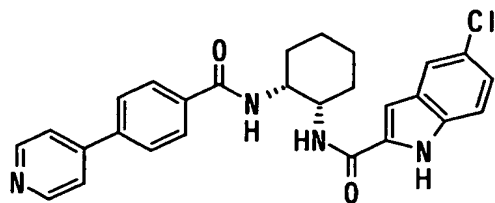
¹H-NMR (DMSO-d₆) δ: 2.33 (3H, s), 2.41-2.50 (1H, m), 2.62-2.73 (3H, m), 2.75-2.81 (1H, m), 2.82 (3H, s), 3.21-3.32 (2H, m), 3.34-3.50 (2H, m), 3.55 (1H, d, J=15.4Hz), 3.63 (1H, d, J=15.4Hz),

4.30-4.40 (0.5H,m), 4.50-4.60 (0.5H,m), 7.04 (1H,s),
 7.15 (1H,dd,J=8.8,2.0Hz), 7.38 (1H,d,J=8.8Hz),
 7.67 (1H,d,J=2.0Hz), 8.49 (1H,d,J=8.5Hz), 8.71 (1H,d,J=8.5Hz),
 11.74 (1H,s).

5 MS (FAB) m/z: 501 (M+H⁺).

[Example 185]

5-Chloro-N-((1R*,2S*)-2-{{4-(pyridin-4-yl)benzoyl}-
 amino}cyclohexyl)indole-2-carboxamide hydrochloride:



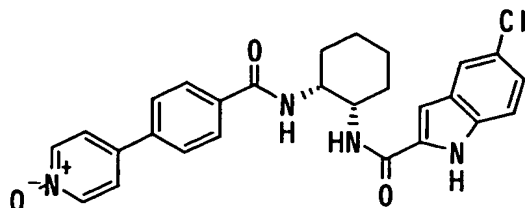
10 The title compound was obtained from the compound
 obtained in Referential Example 71 and the compound
 obtained in Referential Example 237 in a similar manner to
 the process described in Example 2.

¹H-NMR (DMSO-d₆) δ: 1.40-1.52 (2H,m), 1.60-1.80 (4H,m), 1.96-
 15 2.10 (2H,m), 4.24-4.39 (2H,m), 7.15 (1H,dd,J=8.8,2.0Hz),
 7.21 (1H,s), 7.40 (1H,d,J=8.8Hz), 7.64 (1H,d,J=2.0Hz),
 8.06 (4H,s), 8.18 (1H,J=7.3Hz), 8.34-8.42 (3H,m),
 8.94 (2H,d,J=6.9Hz), 11.91 (1H,s).

MS (FAB)m/z: 473 (M+H)⁺.

20 [Example 186]

4-(4-{{((1R*,2S*)-2-{{(5-Chloroindol-2-yl)carbonyl}amino}-
 cyclohexyl)amino}carbonyl}phenyl)pyridine N-oxide:



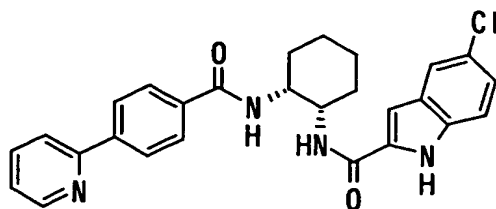
The title compound was obtained from the compound
 obtained in Referential Example 71 and the compound
 obtained in Referential Example 240 in a similar manner to
 5 the process described in Example 2.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.40-1.52 (2H,m), 1.60-1.80 (4H,m), 1.88-
 2.00 (2H,m), 4.21-4.36 (2H,m), 7.12-7.18 (2H,m),
 7.41 (1H,d,J=8.6Hz), 7.66 (1H,s), 7.80-7.87 (4H,m),
 7.91 (2H,d,J=8.3Hz), 8.01 (1H,d,J=7.6Hz), 8.09 (1H,d,J=7.3Hz),
 10 8.27 (2H,d,J=6.6Hz), 11.79 (1H,s).

MS (FAB) m/z : 489 ($\text{M}+\text{H}$) $^+$.

[Example 187]

5-Chloro-N-((1R*,2S*)-2-([4-(pyridin-2-yl)benzoyl]-
 amino)cyclohexyl)indole-2-carboxamide hydrochloride:



15

The title compound was obtained from the compound
 obtained in Referential Example 71 and 4-(2-
 pyridyl)benzoic acid (Japanese Patent Application Laid-
 Open No. 2000-119253) in a similar manner to the process

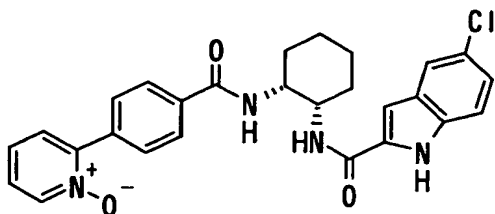
described in Example 2.

¹H-NMR (DMSO-d₆) δ: 1.39-1.51 (2H,m), 1.60-1.80 (4H,m), 1.89-2.00 (2H,m), 4.24-4.38 (2H,m), 7.12-7.16 (2H,m), 7.36-7.39 (1H,m), 7.42 (1H,d,J=8.8Hz), 7.66 (1H,d,J=2.0Hz), 7.87-7.90 (1H,m), 7.92 (2H,d,J=8.3Hz), 7.98-8.11 (3H,m), 8.15 (2H,d,J=8.3Hz), 8.69 (1H,d,J=4.6Hz), 11.80 (1H,s).

MS (FAB) m/z: 473 (M+H)⁺.

[Example 188]

2-(4-{[(1R*,2S*)-2-[(5-Chloroindol-2-yl)carbonyl]amino]-cyclohexyl)amino]carbonyl}phenyl)pyridine N-oxide:



The title compound was obtained from the compound obtained in Referential Example 71 and the compound obtained in Referential Example 241 in a similar manner to the process described in Example 2.

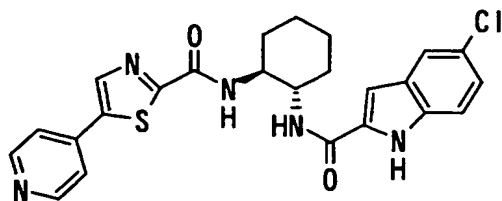
¹H-NMR (DMSO-d₆) δ: 1.39-1.51 (2H,m), 1.60-1.79 (4H,m), 1.89-2.00 (2H,m), 4.23-4.37 (2H,m), 7.12-7.17 (2H,m), 7.39-7.43 (3H,m), 7.61-7.64 (1H,m), 7.67 (1H,d,J=2.0Hz), 7.89 (4H,s), 8.00-8.06 (1H,m), 8.08-8.02 (1H,m), 8.32-8.35 (1H,m), 11.79 (1H,s).

MS (FAB) m/z: 489 (M+H)⁺.

[Example 189]

5-Chloro-N-[(1R*,2R*)-2-([5-(4-pyridin-2-yl)thiazol-2-

yl]carbonyl}amino)cyclohexyl]indole-2-carboxamide
hydrochloride:



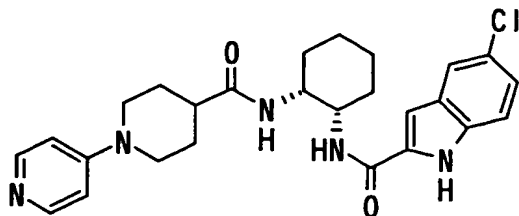
The title compound was obtained from the compound
5 obtained in Referential Example 69 and lithium 5-(4-
pyridyl)thiazole-2-carboxylate (Japanese Patent
Application Laid-Open No. 2000-143623) in a similar manner
to the process described in Example 2.

¹H-NMR (DMSO-d₆) δ: 1.44(2H,br.s), 1.65(4H,br.s), 1.85-
10 2.06(2H,m), 4.23(1H,br.s), 4.30(1H,br.s), 7.14-7.23(2H,m),
7.41(1H,d,J=8.8Hz), 7.69(1H,s), 8.04-8.13(2H,m),
8.13(1H,d,J=8.8Hz), 8.59(1H,d,J=8.0Hz), 8.75-8.87(3H,m),
11.83(1H,s).

MS (ESI)m/z: 480(M+H)⁺.

15 [Example 190]

5-Chloro-N-[(1R*,2S*)-2-({[1-(pyridin-4-yl)piperidin-4-
yl]carbonyl}amino)cyclohexyl]indole-2-carboxamide
hydrochloride:



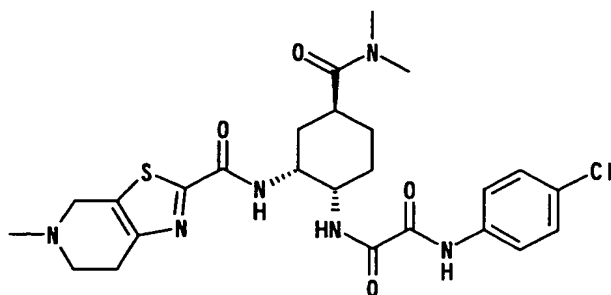
1-(4-Pyridyl)piperidine-4-carboxylic acid
(Tetrahedron, 1998, Vol. 44, p.7095) (206 mg) was
suspended in methylene chloride (50 ml), and thionyl
chloride (144 μ l) was added under ice cooling to stir the
5 mixture for 30 minutes. After triethylamine (969 μ l) was
added to the reaction mixture, the compound (328 mg)
obtained in Referential Example 71 was added to stir the
mixture at room temperature for 30 minutes. The reaction
mixture was concentrated under reduced pressure, water was
10 added to the residue, the mixture was concentrated under
reduced pressure, and precipitate deposited was collected
by filtration to obtain the title compound (310 mg).

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.30-2.00(10H,m), 2.74(1H,br.s),
3.18(2H,q,J=12.3Hz), 4.03(1H,br.s), 4.10-4.25(3H,m), 7.15-
15 7.55(4H,m), 7.42(1H,d,J=8.8Hz), 7.65(1H,s),
7.91(1H,d,J=8.8Hz), 8.20-8.35(3H,m), 11.91(1H,s),
13.47(1H,br.s).

MS (FAB) m/z : 480 (M+H) $^+$.

[Example 191]

20 N^1 -(4-Chlorophenyl)- N^2 -((1S,2R,4S)-4-[(dimethylamino)-
carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide
hydrochloride:



The compound (288 mg) obtained in Referential Example 242 was dissolved in tetrahydrofuran (8.0 ml), lithium hydroxide (46 mg) and water (1.0 ml) were successively
 5 added, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to obtain a crude product (292 mg) of lithium 2-(4-chloroanilino)-2-oxoacetate as a colorless solid. This crude product and the compound obtained in
 10 Referential Example 253 were dissolved in N,N-dimethylformamide (15 ml), and 1-hydroxybenzotriazole monohydrate (164 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (251 mg) were added to stir the mixture at room temperature for 64.5 hours. The
 15 solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation, and the resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was
 20 distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 47:3). The thus-obtained pale yellow

solids were dissolved in methylene chloride, a 1N ethanol solution (0.52 ml) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. Methanol and diethyl ether were added to the residue, and

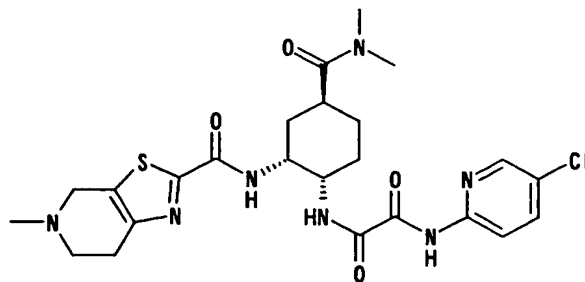
5 precipitate formed was collected by filtration to obtain the title compound (245 mg).

¹H-NMR (DMSO-d₆) δ: 1.45-1.55(1H,m), 1.60-1.80(3H,m), 1.95-2.10(2H,m), 2.79(3H,s), 2.80-3.00(1H,m), 2.92(3H,s), 2.94(3H,s), 3.10-3.40(2H,m), 3.40-3.80(2H,m), 3.95-10
4.05(1H,m), 4.40-4.80(3H,m), 7.40(2H,d,J=8.8Hz), 7.83(2H,d,J=8.8Hz), 8.75(1H,d,J=7.1Hz), 9.00-9.10(1H,br), 10.81(1H,s), 11.45-11.75(1H,m).

MS (FAB) m/z: 547(M+H)⁺.

[Example 192]

15 N¹-(5-Chloropyridin-2-yl)-N²-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino)cyclohexyl)ethanediamide hydrochloride:



20 The compound (240 mg) obtained in Referential Example 243 was dissolved in tetrahydrofuran (8.0 ml), lithium hydroxide (41 mg) and water (1.0 ml) were successively

added to the solution, and the mixture was stirred at room temperature for 2.5 hours. The reaction mixture was concentrated under reduced pressure to obtain lithium 2-[(5-chloropyridin-2-yl)amino]-2-oxoacetate (249 mg).

5 On the other hand, 10% palladium on carbon (200 mg) was added to a solution of the compound (293 mg) obtained in Referential Example 252 in methanol (10 ml), and the mixture was stirred at room temperature for 18 hours under a hydrogen atmosphere. After removing palladium on carbon
10 by filtration, the filtrate was concentrated under reduced pressure to obtain a crude product (259 mg) of N-((1R,2S,5S)-2-amino-5-[(dimethylamino)carbonyl]-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide.

15 This crude product (259 mg) and the lithium salt (249 mg) prepared above were added to N,N-dimethylformamide (15 ml), and 1-hydroxybenzotriazole monohydrate (166 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (235 mg) were added to stir the mixture at
20 room temperature for 63.5 hours. The solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation, and the resultant organic layer was dried over anhydrous sodium
25 sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol

= 93:7). The thus-obtained pale yellow solids were dissolved in methylene chloride, a 1N ethanol solution (0.855 ml) of hydrochloric acid was added to the solution, and the solvent was distilled off under reduced pressure.

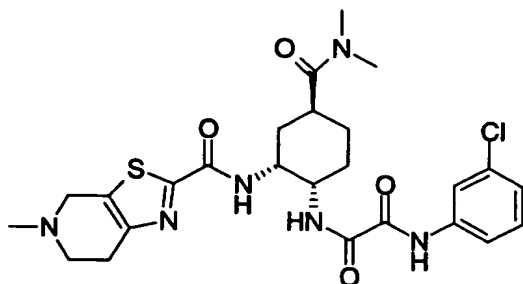
5 Methanol and diethyl ether were added to the residue, and precipitate formed was collected by filtration to obtain the title compound (209 mg).

¹H-NMR (DMSO-d₆) δ: 1.40-1.57(1H,m), 1.60-1.80(3H,m), 1.95-2.13(2H,m), 2.79(3H,s), 2.80-3.00(1H,m), 2.92(3H,s),
10 2.94(3H,s), 3.10-3.40(2H,m), 3.40-3.80(2H,m), 3.95-4.05(1H,m), 4.37-4.80(3H,m), 7.90-8.10(2H,m), 8.45(1H,d,J=2.2Hz), 8.71(1H,d,J=7.6Hz), 9.10-9.30(1H,br), 10.26(1H,s), 11.30-11.60(1H,br).

MS (FAB) m/z: 548 (M+H)⁺.

15 [Example 193]

N¹-(3-Chlorophenyl)-N²-((1S,2R,4S)-4-[(dimethylamino)-carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide hydrochloride:



20

The compound (222 mg) obtained in Referential Example 270 and 3-chloroaniline (63 μl) were dissolved in N,N-

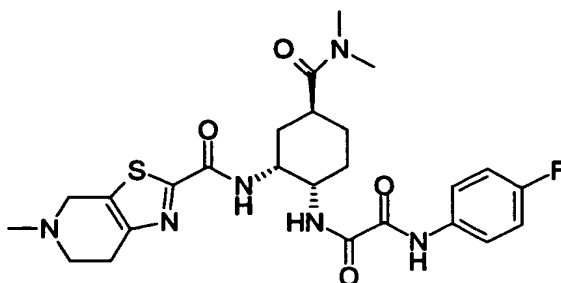
dimethylformamide (10 ml), and 1-hydroxybenzotriazole monohydrate (68 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (144 mg) were added to stir the mixture at room temperature for 40 hours. The solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation, and the resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 30:1). The thus-obtained pale yellow solids were dissolved in methylene chloride, a 1N ethanol solution (0.50 ml) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. Diethyl ether was added to the residue, and precipitate formed was collected by filtration to obtain the title compound (174 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.45-1.62(1H,m), 1.65-1.90(3H,m), 1.98-2.20(2H,m), 2.79(3H,s), 2.88-3.10(1H,m), 2.93(3H,s), 2.94(3H,s), 3.15-3.40(2H,m), 3.40-3.90(2H,m), 3.95-4.10(1H,m), 4.40-4.80(3H,m), 7.19(1H,dd,J=9.3,2.0Hz), 7.37(1H,d,J=8.2Hz), 7.77(1H,d,J=8.3Hz), 7.92-8.05(1H,m), 8.75(1H,d,J=7.3Hz), 8.95-9.20(1H,br), 10.87(1H,s), 11.25-11.45(1H,br).

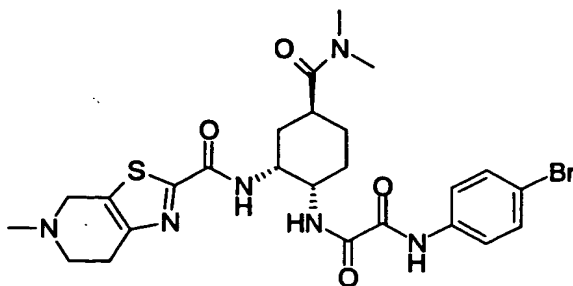
[Example 194]

N^1 -((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-[(5-methyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino)cyclohexyl)-N²-(4-fluorophenyl)-ethanediamide hydrochloride:



- 5 The title compound was obtained by hydrolyzing the compound obtained in Referential Example 254, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process
- 10 described in Example 191.
- ¹H-NMR (DMSO-d₆) δ: 1.40-2.13(6H,m), 2.77(3H,s), 2.93(3H,s), 2.97(3H,s), 3.12-3.82(7H,m), 3.93-4.04(1H,m), 4.38-4.46(1H,m), 4.35-4.75(1H,m), 7.11-7.21(2H,m), 7.72-7.84(2H,m), 8.73(1H,d,J=7.6Hz), 8.93-9.02(1H,m),
- 15 10.70(1H,s).
- MS (FAB) m/z: 531(M+H)⁺.
- [Example 195]
- N¹-(4-Bromophenyl)-N²-((1S,2R,4S)-4-[(dimethylamino)-carbonyl]-2-[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
- 20 pyridin-2-yl)carbonyl]amino)cyclohexyl)ethanediamide hydrochloride:



The compound (152 mg) obtained in Referential Example 255 was dissolved in tetrahydrofuran (5.0 ml), a 1N aqueous solution (1.20 ml) of sodium hydroxide and
 5 methanol (5.0 ml) were successively added, and the mixture was stirred at room temperature for 2.5 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride (10 ml) and 1N hydrochloric acid (2.0 ml) were added to the residue to conduct liquid
 10 separation. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to obtain a crude product (280 mg) of 2-(4-bromoanilino)-2-oxoacetic acid as a colorless solid. This crude product and the compound (280 mg)
 15 obtained in Referential Example 253 were dissolved in N,N-dimethylformamide (30 ml), and 1-hydroxybenzotriazole monohydrate (90 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (226 mg) were added to stir the mixture at room temperature for a night. The
 20 solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct

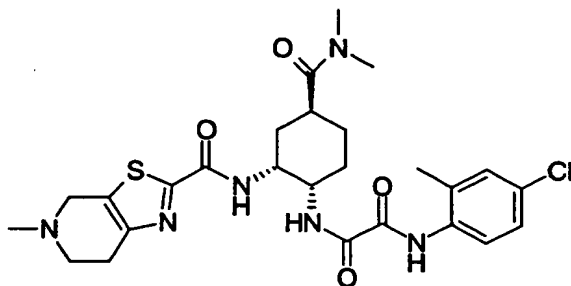
liquid separation, and the resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 97:3). The thus-obtained pale yellow solids were dissolved in methylene chloride, a 1N ethanol solution (191 μ l) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. Methanol and diethyl ether were added to the residue, and precipitate formed was collected by filtration to obtain the title compound (103 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.43-1.57(1H,m), 1.59-1.80(3H,m), 1.97-2.10(2H,m), 2.79(3H,s), 2.84-2.98(7H,m), 3.18(2H,br.s), 3.39-3.72(2H,m), 3.95-4.05(1H,m), 4.20-4.80(3H,m), 7.53(2H,d,J=8.8Hz), 7.77(2H,d,J=8.8Hz), 8.75(1H,d,J=7.3Hz), 8.97-9.09(1H,m), 10.82(1H,s), 11.11(1H,br.s).

MS (FAB) m/z : 591(M+H) $^+$.

[Example 196]

N^1 -(4-Chloro-2-methylphenyl)- N^2 -((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino)cyclohexyl)ethanediamide hydrochloride:



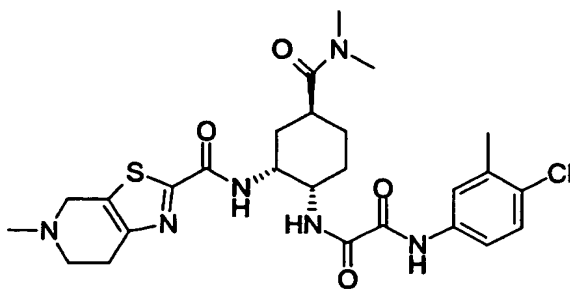
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 256, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 191.

¹H-NMR (DMSO-d₆) δ: 1.45-1.55 (1H,m), 1.60-1.80 (3H,m), 2.00-2.10 (2H,m), 2.19 (3H,s), 2.79 (3H,s), 2.80-3.00 (7H,m), 3.31 (2H,br.s), 3.40-3.70 (2H,br), 3.95-4.05 (1H,m), 4.35-4.70 (3H,m), 7.20-7.30 (1H,m), 7.35 (1H,d,J=2.5Hz), 7.43 (1H,d,J=8.6Hz), 8.76 (1H,d,J=6.6Hz), 9.00-9.15 (1H,br), 10.19 (1H,s).

MS (FAB) m/z: 561 (M+H)⁺.

[Example 197]

N¹-(4-Chloro-3-methylphenyl)-N²-((1S,2R,4S)-4-((dimethylamino)carbonyl)-2-((5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl)-amino)cyclohexyl)ethanediamide hydrochloride:



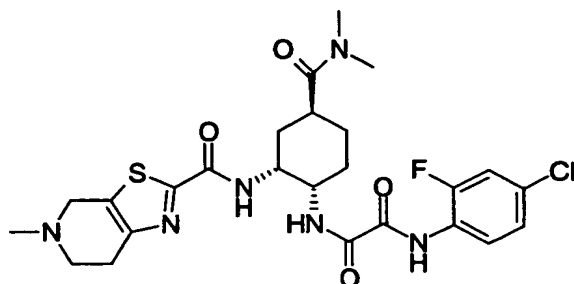
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 257, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 191.

¹H-NMR (DMSO-d₆) δ: 1.47-1.53(1H,m), 1.68-1.80(3H,m), 1.98-2.09(2H,m), 2.29(3H,s), 2.79(3H,s), 2.80-3.00(1H,m), 2.95(6H,s), 3.17-3.19(3H,m), 3.40-3.80(1H,m), 3.93-4.02(1H,m), 4.44-4.56(3H,m), 7.38(1H,d,J=8.8Hz), 7.65(1H,d,J=8.8Hz), 7.74(1H,s), 8.75(1H,d,J=7.8Hz), 8.96(1H,d,J=8.0Hz), 10.69(1H,s).

MS (FAB) m/z: 561(M+H)⁺.

[Example 198]

N¹-(4-Chloro-2-fluorophenyl)-N²-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]-amino)cyclohexyl)ethanediamide hydrochloride:



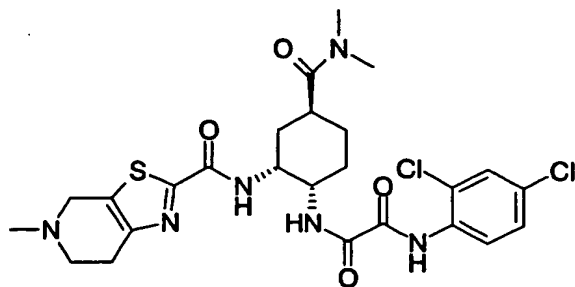
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 258, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 191.

¹H-NMR (DMSO-d₆) δ: 1.40-1.55(1H,m), 1.58-1.80(3H,m), 1.95-2.12(2H,m), 2.77(3H,s), 2.80-3.00(1H,m), 2.91(3H,s), 2.92(3H,s), 3.10-3.40(2H,m), 3.40-3.80(2H,m), 3.95-4.05(1H,m), 4.30-4.80(3H,m), 7.29(1H,d,J=8.5Hz), 7.52(1H,dd,J=10.3,2.0Hz), 7.61(1H,t,J=8.4Hz), 8.72(1H,d,J=6.8Hz), 9.00-9.20(1H,br), 10.38(1H,s), 11.20-11.45(1H,br).

MS (FAB) m/z: 565(M+H)⁺.

[Example 199]

N¹-(2,4-Dichlorophenyl)-N²-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino)cyclohexyl)ethanediamide hydrochloride:



The compound (300 mg) obtained in Referential Example
 270 was dissolved in N,N-dimethylformamide (5 ml), and
 2,4-dichloroaniline (165 mg), 1-(3-dimethylaminopropyl)-3-
 5 ethylcarbodiimide hydrochloride (260 mg) and 1-
 hydroxybenzotriazole monohydrate (91 mg) were added to
 stir the mixture at room temperature for 2 days. The
 solvent was distilled off under reduced pressure, a
 saturated aqueous solution of sodium hydrogencarbonate and
 10 methylene chloride were added to the residue to conduct
 liquid separation, and the resultant organic layer was
 dried over anhydrous sodium sulfate. After the solvent was
 distilled off under reduced pressure, the residue was
 purified by column chromatography on silica gel (methylene
 15 chloride:methanol = 47:3) to obtain a free base of the
 title compound. This product was dissolved in methylene
 chloride, a 1N ethanol solution (108 μ l) of hydrochloric
 acid was added, and the solvent was distilled off under
 reduced pressure. A small amount of methanol was added to
 20 the residue, and diethyl ether was added dropwise while
 irradiating with ultrasonic waves to collect precipitate
 formed by filtration. This product was washed with diethyl

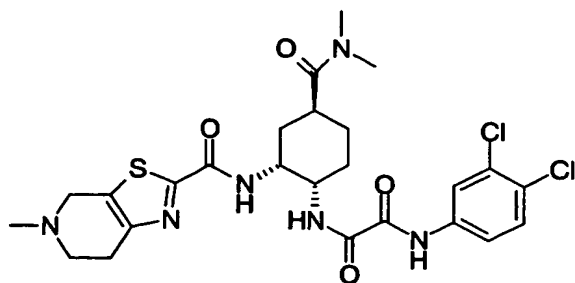
ether to obtain the title compound (60 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.45-1.77 (4H,m), 2.03-2.12 (2H,m),
2.79 (3H,s), 2.92-2.96 (7H,m), 3.25 (2H,br.s), 3.49 (1H,br.s),
3.69 (1H,br.s), 3.98-4.04 (1H,m), 4.40-4.43 (1H,m),
5 4.45 (1H,br.s), 4.69 (1H,br.s), 7.48 (1H,dd, $J=8.5, 2.4\text{Hz}$),
7.75 (1H,d, $J=2.4\text{Hz}$), 7.89 (1H,d, $J=8.5\text{Hz}$), 8.75 (1H,d, $J=6.8\text{Hz}$),
9.21 (1H,br.s), 10.25 (1H,s), 11.55 (1H,br.s).

MS (FAB) m/z : 581 ($\text{M}+\text{H}$) $^+$.

[Example 200]

10 N^1 -(3,4-Dichlorophenyl)- N^2 -((1S,2R,4S)-4-[(dimethylamino)-
carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridin-2-yl)carbonyl]amino)cyclohexyl)ethanediamide:



3,4-Dichloroaniline (1.62 g) was dissolved in
15 methylene chloride (20 ml), and triethylamine (1.67 ml)
and methyl chlorooxoacetate (1.01 ml) were successively
added under ice cooling, and the mixture was stirred at
room temperature for 21 hours. Water and methylene
chloride were added to the reaction mixture to conduct
20 liquid separation. The resultant water layer was extracted
with methylene chloride. Organic layers were combined and
dried over anhydrous magnesium sulfate, and the solvent

was distilled off under reduced pressure. The resultant residue was dissolved in ethanol (50 ml), and water (25 ml) and lithium hydroxide monohydrate (629 mg) were successively added to stir the mixture at room temperature for 12.5 hours. Lithium hydroxide monohydrate (629 mg) was additionally added to stir the mixture at room temperature for 5.5 hours. The reaction mixture was concentrated under reduced pressure to solidity. Water and diethyl ether were added to the residue to conduct liquid separation.

Hydrochloric acid was added to the resultant water layer to acidify it. Solid formed were collected by filtration to obtain a crude product (1.62 g) of 2-(3,4-dichloroanilino)-2-oxoacetic acid as a colorless solid. This crude product (191 mg) and the compound obtained in Referential Example 253 were dissolved in N,N-dimethylformamide (10 ml), and 1-hydroxybenzotriazole monohydrate (110 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (157 mg) were added to stir the mixture at room temperature for 67 hours. The solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and ethyl acetate were added to the residue to conduct liquid separation, and the resultant water layer was extracted 3 times with methylene chloride. Organic layers were combined and dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica

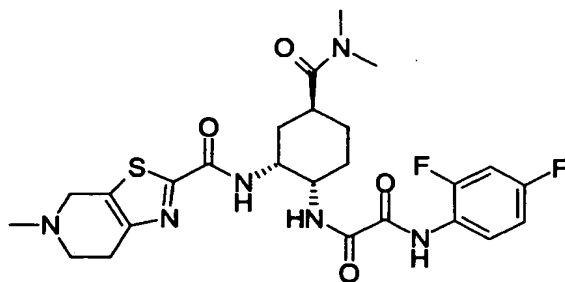
gel (methylene chloride:methanol = 95:5) to obtain the title compound (154 mg).

¹H-NMR (CDCl₃) δ: 1.77-1.88 (1H,m), 1.91-1.95 (1H,m), 2.05-2.10 (3H,m), 2.51 (3H,s), 2.77-2.99 (6H,m), 2.95 (3H,s),
5 3.05 (3H,s), 3.68 (1H,d,J=15.5Hz), 3.74 (1H,d,J=15.5Hz),
4.08-4.13 (1H,m), 4.69-4.72 (1H,m), 7.40 (2H,s),
7.41 (1H,d,J=7.7Hz), 7.90 (1H,s), 8.01 (1H,d,J=7.7Hz),
9.27 (1H,s).

MS (ESI) m/z: 581 (M+H)⁺.

10 [Example 201]

N¹-(2,4-Difluorophenyl)-N²-((1S,2R,4S)-4-[(dimethylamino)-carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide:



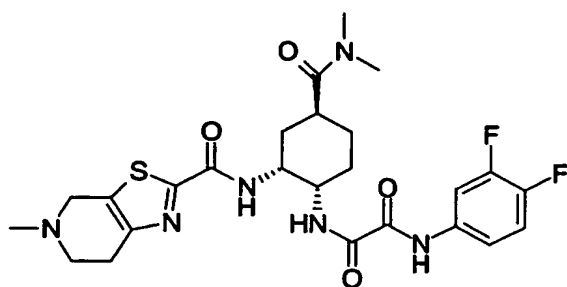
15 The title compound was obtained by hydrolyzing the compound obtained in Referential Example 259 and condensing the hydrolyzate with the compound obtained in Referential Example 253 in a similar manner to the process described in Example 191.

20 ¹H-NMR (CDCl₃) δ: 1.55-1.62 (1H,m), 1.67-1.98 (2H,m), 2.01-2.18 (4H,m), 2.52 (3H,s), 2.77-3.00 (4H,m),
2.95 (3H,s), 2.99 (3H,s), 3.65-3.78 (2H,m), 4.06-4.15 (1H,m),

4.66-4.73 (1H,m), 6.85-6.94 (2H,m), 7.38 (1H,d,J=8.5Hz),
7.96 (1H,d,J=7.3Hz), 8.22-8.29 (1H,m), 9.36 (1H,br).

[Example 202]

N¹-(3,4-Difluorophenyl)-N²-((1S,2R,4S)-4-[(dimethylamino)-
5 carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridin-2-yl) carbonyl] amino)cyclohexyl)ethanediamide:



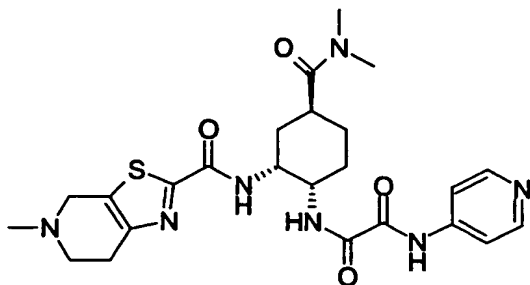
The title compound was obtained by hydrolyzing the
compound obtained in Referential Example 260 and
10 condensing the hydrolyzate with the compound obtained in
Referential Example 253 in a similar manner to the process
described in Example 191.

¹H-NMR (CDCl₃) δ: 1.56-1.73 (1H,m), 1.77-1.99 (2H,m), 2.00-
2.18 (4H,m), 2.52 (3H,s), 2.75-3.00 (4H,m), 2.95 (3H,s),
15 3.06 (3H,s), 3.64-3.79 (2H,m), 4.05-4.14 (1H,m), 4.68-
4.75 (1H,m), 7.09-7.21 (2H,m), 7.38 (1H,d,J=8.8Hz),
7.72 (1H,ddd,J=12.0, 7.1,2.6Hz), 7.95 (1H,d,J=7.8Hz),
9.22 (1H,br).

[Example 203]

20 N¹-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-[[(5-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-
amino)cyclohexyl)-N²-(pyridin-4-yl)ethanediamide

hydrochloride:



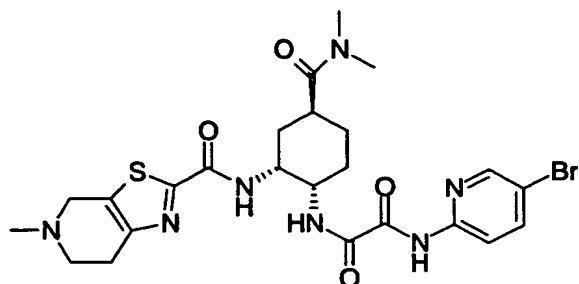
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 261, condensing
5 the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 191.

¹H-NMR (DMSO-d₆) δ: 1.40-2.10 (6H, m), 2.77 (3H, s), 2.927 (3H, s),
10 2.933 (3H, s), 3.05-4.20 (8H, m), 4.40-4.55 (1H, m),
8.27 (2H, d, J=6.8 Hz), 8.67 (1H, d, J=8.0 Hz), 8.71 (2H, d, J=6.8 Hz),
9.10-9.30 (1H, br), 11.81 (1H, s).

MS (FAB) m/z: 514 (M+H)⁺.

[Example 204]

15 N¹-(5-Bromopyridin-2-yl)-N²-((1S,2R,4S)-4-[(dimethylamino)-
carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridin-2-yl) carbonyl] amino} cyclohexyl) ethanediamide
hydrochloride:



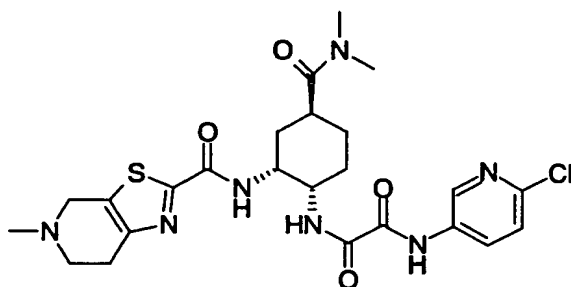
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 262, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 195.

¹H-NMR (DMSO-d₆) δ: 1.43-1.57(1H,m), 1.61-1.81(3H,m), 1.98-2.15(2H,m), 2.79(3H,s), 2.86(3H,s), 2.89-3.01(4H,m), 3.18(2H,br.s), 3.50(2H,br.s), 3.95-4.05(1H,m), 4.35-4.62(3H,m), 7.97(1H,d,J=9.0Hz), 8.12(1H,dd,J=9.0,2.4Hz), 8.52(1H,d,J=2.4Hz), 8.70(1H,d,J=7.5Hz), 9.18(1H,d,J=7.5Hz), 10.25(1H,br.s).

MS (FAB) m/z: 592 (M+H)⁺.

15 [Example 205]

N¹-(6-Chloropyridin-3-yl)-N²-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino)-cyclohexyl)ethanediamide hydrochloride:



The compound (200 mg) obtained in Referential Example 263, which was a crude product, was dissolved in methanol (10 ml) to heat the solution to 50°C, and a 1N aqueous solution (3 ml) of sodium hydroxide to stir the mixture for 5 minutes. To this mixture was added 1N hydrochloric acid to adjust the pH to a weak acidity. The solvent was distilled off under reduced pressure to obtain residue containing 2-[(2-chloropyridin-5-yl)amino]-2-oxoacetic acid. This residue and the compound (250 mg) obtained in Referential Example 253 were dissolved in N,N-dimethylformamide (5 ml), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (328 mg) and 1-hydroxybenzotriazole monohydrate (46 mg) were added to stir the mixture at room temperature for 3 days. The solvent was distilled off under reduced pressure, and a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene

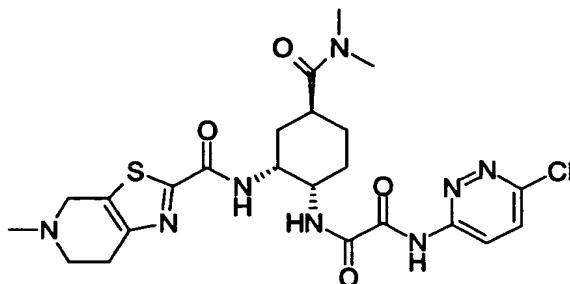
chloride:methanol = 47:3) to obtain a free base of the title compound as a pale yellow solid. This product was dissolved in methylene chloride, a 1N ethanol solution (862 μ l) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. A small amount of methanol was added to the residue, and ethyl acetate and diethyl ether were added dropwise while irradiating with ultrasonic waves to collect precipitate formed by filtration. This product was washed with diethyl ether to obtain the title compound (229 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.46-1.75(4H,m), 1.99-2.09(2H,m), 2.79(3H,s), 2.92-2.95(7H,m), 3.12-3.53(3H,m), 3.70(1H,br.s), 3.99-4.06(1H,m), 4.44(2H,br.s), 4.69,4.73(1H,each s), 7.53(1H,d,J=8.5Hz), 8.23-8.25(1H,m), 8.72-8.77(1H,m), 8.85(1H,s), 9.07,9.16(1H,each d,J=8.1Hz), 11.09(1H,d,J=8.1Hz), 11.78(1H,br.s).

MS (FAB) m/z : 548 ($\text{M}+\text{H}$) $^+$.

[Example 206]

N^1 -(6-Chloropyridazin-3-yl)- N^2 -((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino}cyclohexyl)ethanediamide hydrochloride:



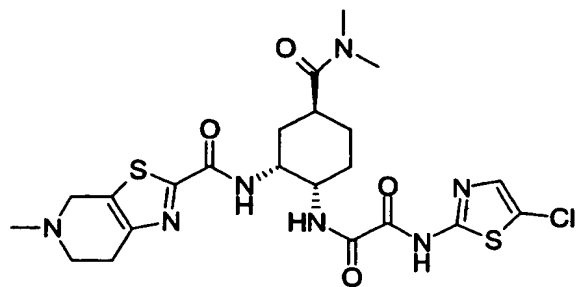
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 264, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 191.

¹H-NMR (DMSO-d₆) δ: 1.44-1.57(1H,m), 1.62-1.80(3H,m), 2.00-2.10(2H,m), 2.79(3H,s), 2.86(3H,br.s), 2.94(3H,s), 2.95-3.01(1H,m), 3.14-3.23(2H,m), 3.45-3.63(2H,m), 3.96-4.08(1H,m), 4.40-4.60(3H,m), 7.97(1H,d,J=9.3Hz), 8.26(1H,d,J=9.3Hz), 8.69(1H,d,J=7.6Hz), 9.20(1H,d,J=7.6Hz), 11.06(1H,s).

MS (FAB) m/z: 549(M+H)⁺.

[Example 207]

N¹-(5-Chlorothiazol-2-yl)-N²-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino)cyclohexyl)ethanediamide hydrochloride:



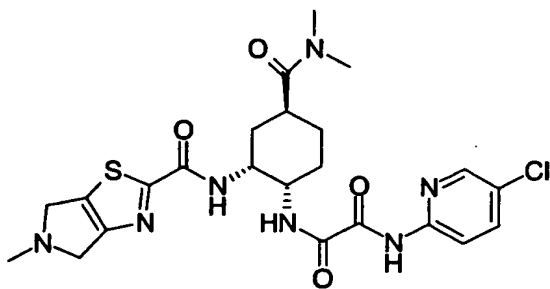
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 265, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 191.

¹H-NMR (DMSO-d₆) δ: 1.35-2.10 (6H,m), 2.77 (3H,s), 2.92 (3H,s), 2.93 (3H,s), 3.05-4.23 (8H,m), 4.32-4.80 (2H,m), 7.59 (1H,s), 8.63 (1H,d,J=7.6Hz), 9.14 (1H,d,J=7.6Hz).

MS (FAB) m/z: 554 (M+H)⁺.

[Example 208]

N¹-(5-Chloropyridin-2-yl)-N²-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)carbonyl]amino)cyclohexyl)ethanediamide hydrochloride:



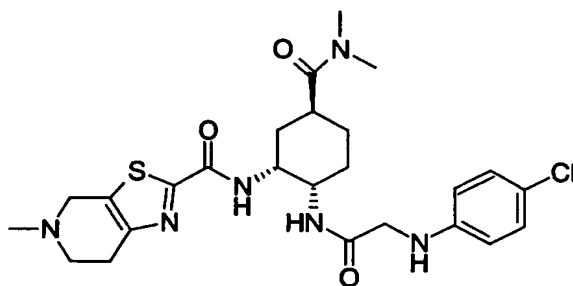
The compound (210 mg) obtained in Referential Example 266 and the compound (350 mg) obtained in Referential Example 272 were dissolved in N,N-dimethylformamide (15 ml), and 1-hydroxybenzotriazole monohydrate (205 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (290 mg) were added to stir the mixture at room temperature for 20 hours. The solvent was distilled off under reduced pressure, and a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1). The thus-obtained pale yellow solids were dissolved in methylene chloride, a 1N ethanol solution (0.46 ml) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. Methanol and diethyl ether were added to the residue, and precipitate formed was collected by filtration to obtain the title compound (248 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.47-1.50 (1H,m), 1.69-1.76 (3H,m), 1.98-2.06 (2H,m), 2.79 (3H,s), 2.95 (3H,s), 2.98-3.05 (1H,m), 3.10 (3H,s), 3.49-4.62 (6H,m), 7.98-8.03 (2H,m), 8.45 (1H,s), 8.73 (1H,d,J=7.6Hz), 9.10 (1H,d,J=8.0Hz), 10.30 (1H,s).

MS (FAB) m/z : 534 ($\text{M}+\text{H}$) $^+$.

[Example 209]

N-((1R,2S,5S)-2-((2-(4-chloroanilino)acetyl)amino)-5-((dimethylamino)carbonyl)cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



5

The compound (2.3 g) obtained in Referential Example 267 was dissolved in ethanol (10 ml), and a 1N aqueous solution (20 ml) of sodium hydroxide was added to stir the mixture at room temperature for 2 hours. After 1N hydrochloric acid (20 ml) was added to the reaction mixture, the mixture was diluted with water and stirred for 30 minutes. Insoluble matter deposited was collected by filtration to obtain 2-(4-chloroanilino)acetic acid (1.05 g) as a colorless solid. This solid and the compound (0.25 g) obtained in Referential Example 253 were dissolved in N,N-dimethylformamide (10 ml), and 1-hydroxybenzotriazole monohydrate (0.11 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.23 g) were added to stir the mixture at room temperature for 4 days. After the reaction mixture was diluted with chloroform and washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated

10

15

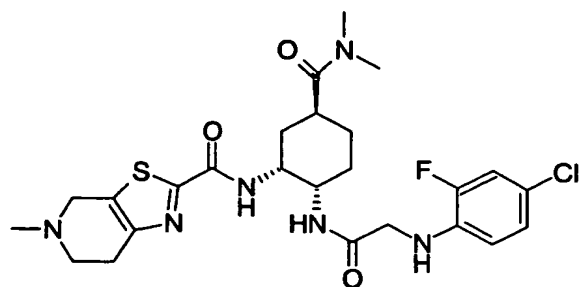
20

aqueous solution of sodium chloride, the resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (chloroform:methanol = 97:3). The thus-obtained pale yellow solid was dissolved in ethanol, a 1N ethanol solution of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. Methanol and diethyl ether were added to the residue, and precipitate formed was collected by filtration to obtain the title compound (0.15 g).

¹H-NMR (DMSO-d₆) δ: 1.35-1.41(1H,m), 1.59-1.80(3H,m), 1.82-1.95(2H,m), 2.76(3H,s), 2.93(3H,s), 2.94(3H,s), 2.99-3.10(1H,m), 3.10-3.22(2H,m), 3.42-3.60(2H,m), 3.60-3.77(2H,m), 3.80-3.90(1H,m), 4.35-4.48(2H,m), 4.68-4.80(1H,m), 6.40(1H,d,J=6.7Hz), 6.44(1H,d,J=6.7Hz), 6.90(1H,d,J=6.7Hz), 7.00(1H,d,J=6.7Hz), 7.70-7.89(1H,m), 8.35-8.42(1H,m), 11.05-11.38(1H,m).

[Example 210]

N-{(1R,2S,5S)-2-([2-(4-Chloro-2-fluoroanilino)-acetyl]amino)-5-[(dimethylamino)carbonyl]cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:

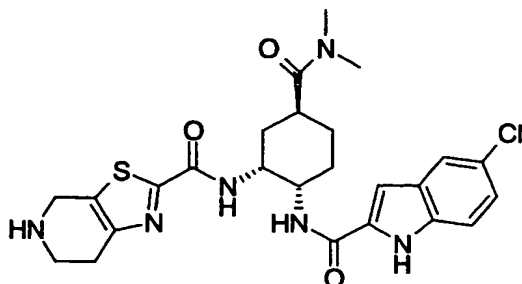


The title compound was obtained by hydrolyzing the compound obtained in Referential Example 268, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 209.

¹H-NMR (DMSO-d₆) δ: 1.35-1.42 (1H,m), 1.55-1.78 (3H,m), 1.80-2.00 (2H,m), 2.76 (3H,s), 2.92 (3H,s), 2.94 (3H,s), 2.99-3.10 (1H,m), 3.10-3.22 (2H,m), 3.42-3.60 (2H,m), 3.60-3.77 (2H,m), 3.85-4.00 (1H,m), 4.33-4.48 (2H,m), 4.65-4.80 (1H,m), 6.41 (1H,t,J=8.8Hz), 6.73 (1H,dt,J=8.8,1.2Hz), 7.08 (1H,dd,J=11.7,1.2Hz), 7.78-7.92 (1H,m), 8.35-8.42 (1H,m), 11.18-11.50 (1H,m).

[Example 211]

N-{(1R,2S,5S)-2-[[(5-Chloroindol-2-yl)carbonyl]amino]-5-[(dimethylamino)carbonyl]cyclohexyl}-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained by condensing the compound obtained in Referential Example 432 with the compound obtained in Referential Example 34 and then

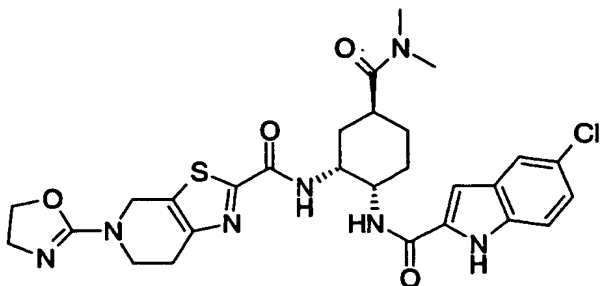
5 treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 2.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.45-1.60 (1H,m), 1.70-2.15 (6H,m),
2.80 (3H,s), 2.97 (3H,s), 2.95-3.15 (2H,m), 3.35-3.55 (2H,m),
4.05-4.20 (1H,m), 4.46 (2H,s), 4.50-4.65 (1H,m), 7.05 (1H,s),
10 7.16 (1H,dd,J=8.8,2.2Hz), 7.41 (1H,d,J=8.8Hz), 7.68 (1H,s),
8.30-8.45 (1H,br), 9.30-9.50 (1H,br), 11.78 (1H,s).

MS (ESI) m/z : 529 ($\text{M}+\text{H}$) $^+$.

[Example 212]

N-((1R,2S,5S)-2-({[(5-Chloroindol-2-yl)carbonyl]amino}-5-
15 [(dimethylamino)carbonyl]cyclohexyl)-5-(4,5-dihydrooxazol-
2-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-
carboxamide:

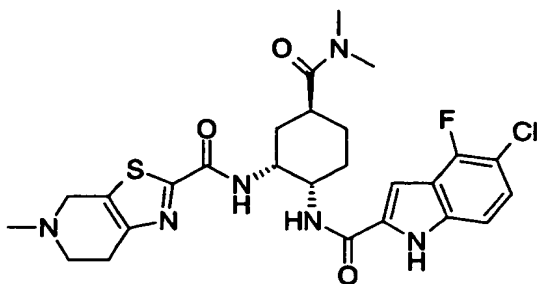


The compound (250 mg) obtained in Example 211 was suspended in methylene chloride, and a saturated aqueous solution of sodium hydrogencarbonate was added to fully stir the mixture. The resultant organic layer was separated and dried over anhydrous magnesium sulfate. Triethylamine (0.5 ml) and bromoethyl isocyanate (43 μ l) were then added to stir the mixture at room temperature for 20 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to separate an organic layer. The organic layer was dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 22:3) to obtain the title compound (227 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50-2.15(4H,m), 2.15-2.40(2H,m), 2.80-3.00(1H,m), 2.97(3H,s), 3.11(3H,s), 3.70-3.95(4H,m), 4.10-4.30(1H,m), 4.30-4.50(2H,m), 4.60-4.70(1H,m), 4.74(2H,s), 6.85(1H,s), 7.21(1H,dd, $J = 8.8, 2.2\text{Hz}$), 7.34(1H,d, $J = 8.8\text{Hz}$), 7.50(1H,br.s), 7.62(1H,s), 7.87(1H,br.s), 9.48(1H,br.s). MS (ESI) m/z : 598(M+H) $^+$.

[Example 213]

N-{(1R,2S,5S)-2-[[(5-Chloro-4-fluoroindol-2-yl)carbonyl]amino]-5-[(dimethylamino)carbonyl]cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (140 mg) obtained in Referential Example 144 was dissolved in N,N-dimethylformamide (10 ml), and the compound (100 mg) obtained in Referential Example 274, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (140 mg) and 1-hydroxybenzotriazole monohydrate (110 mg) were added to stir the mixture at room temperature for 18 hours. The solvent was distilled off under reduced pressure, and the residue was partitioned in water-ethyl acetate, and a water layer was extracted with ethyl acetate. The resultant organic layers were combined, washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 1:19), giving tert-butyl (1R,2S,5S)-2-[[(5-chloro-4-

fluoroindol-2-yl)carbonyl]amino}-5-

[(dimethylamino)carbonyl]cyclohexylcarbamate (260 mg).

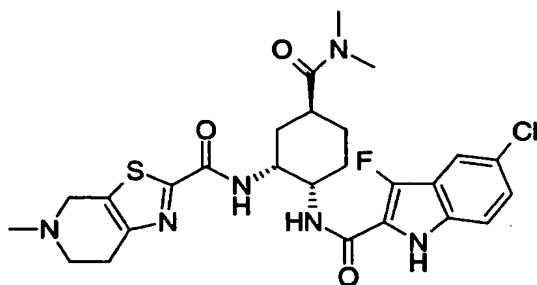
The thus-obtained powder was dissolved in methylene chloride (5 ml), and a 4N dioxane solution (1.2 ml) of
5 hydrochloric acid was added. After the reaction mixture was stirred at room temperature for 3.5 hours, the solvent was distilled off under reduced pressure. Methylene chloride (10 ml) was added to the residue, and the mixture was concentrated. After this process was repeated 3 times,
10 the residue was dried under reduced pressure to obtain crude N-{(1S,2R,4S)-2-amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-5-chloro-4-fluoroindole-2-carboxamide. This product was dissolved in N,N-dimethylformamide (50 ml), and the compound (150 mg) obtained in Referential Example
15 10, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (140 mg) and 1-hydroxybenzotriazole monohydrate (110 mg) were added to stir the mixture at room temperature for 18 hours. The solvent was distilled off under reduced pressure, and the residue was
20 partitioned in a mixed solvent of water-ethyl acetate-tetrahydrofuran, and a water layer was extracted with ethyl acetate. The resultant organic layers were combined, washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent
25 was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 1:19) to obtain a free base

of the title compound (270 mg). This product was dissolved in methylene chloride (10 ml), and a 1N ethanol solution (0.72 ml) of hydrochloric acid was added to stir the mixture at room temperature for 30 minutes. Crystals deposited were collected by filtration to obtain the title compound (200 mg).

¹H-NMR (DMSO-d₆) δ: 1.24-1.98 (6H,m), 2.33-3.33 (6H,m), 2.81 (3H,s), 2.90 (3H,s), 2.99 (3H,s), 4.12 (1H, br.s), 4.30-4.70 (1H,m), 4.60 (1H,br.s), 7.21 (1H,s), 7.27 (2H,br.s), 8.37 (1H,d,J=8.1Hz), 8.43 (1H,d,J=7.6Hz), 12.11 (1H,s).
MS (FAB) m/z: 561 (M+H)⁺.

[Example 214]

N-((1R,2S,5S)-2-((5-Chloro-3-fluoroindol-2-yl)carbonyl)amino)-5-((dimethylamino)carbonyl)cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (250 mg) obtained in Referential Example 279 was dissolved in methylene chloride (60 ml), and a 4N dioxane solution (1.3 ml) of hydrochloric acid was added. After the reaction mixture was stirred at room temperature for 5.5 hours, a 4N dioxane solution (0.65 ml) of

hydrochloric acid was additionally added, and the mixture was stirred at room temperature for 1 hour. The solvent was distilled off under reduced pressure, methylene chloride (10 ml) was added to the residue, and the mixture was concentrated. This process was repeated 3 times. The residue was dried under reduced pressure, and the thus-obtained crude product was dissolved in N,N-dimethylformamide (50 ml), and the compound (160 mg) obtained in Referential Example 10, 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (150 mg) and 1-hydroxybenzotriazole monohydrate (120 mg) were added to stir the mixture at room temperature for 18 hours. The solvent was distilled off under reduced pressure, and the residue was partitioned in a mixed solvent of water-ethyl acetate, and a water layer was extracted with ethyl acetate. The resultant organic layers were combined, washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified twice by column chromatography on silica gel (methanol:methylene chloride = 2:23 → 1:9) to obtain a free base (260 mg) of the title compound. This product was dissolved in methylene chloride, and a 1N ethanol solution (0.69 ml) of hydrochloric acid was added to stir the mixture at room temperature for 30 minutes. The solvent was distilled off. The residue was dissolved in methanol, and diethyl ether and hexane were added. The thus-obtained

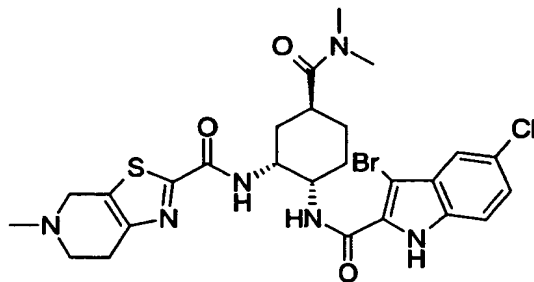
crystals were collected by filtration to obtain the title compound (230 mg).

¹H-NMR (DMSO-d₆) δ: 1.50-1.56(1H,m), 1.73-1.78(3H,m), 1.94-2.02(2H,m), 2.33-3.55(6H,m), 2.80(3H,s), 2.92(3H,s),
5 2.98(3H,s), 4.17(1H,br.s), 4.30-4.80(1H,br), 4.62(1H,br.s),
7.25(1H,d,J=8.8,1.7Hz), 7.40(1H,d,J=8.8,1.7Hz),
7.65(1H,d,J=1.7Hz), 7.72(1H,d,J=5.9Hz), 8.74(1H,d,J=8.0Hz),
10.85-11.35(1H,br), 11.71(1H,s).

MS (FAB) m/z: 561(M+H)⁺.

10 [Example 215]

N-((1R,2S,5S)-2-([(3-Bromo-5-chloroindol-2-yl)carbonyl]-amino)-5-[(dimethylamino)carbonyl]cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



15

The title compound was obtained by treating the compound obtained in Referential Example 282 with a 4N dioxane solution of hydrochloric acid and condensing the thus treated compound with the compound obtained in
20 Referential Example 10 in a similar manner to the process described in Example 214.

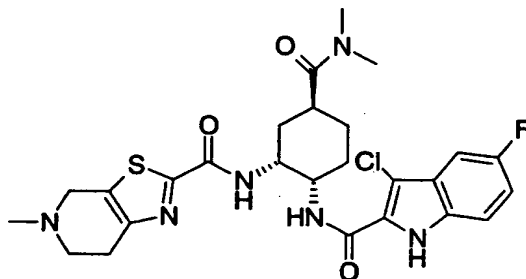
¹H-NMR (DMSO-d₆) δ: 1.51-2.01(6H,m), 2.33-3.29(7H,m),

2.81(3H,s), 2.88(3H,s), 3.01(3H,s), 4.20(1H,br.s),
4.48(1H,br), 4.70-4.73(1H,m), 7.29(1H,dd,J=8.9,1.8Hz),
7.45-7.49(2H,m), 7.80(1H,d,J=7.6Hz), 8.76(1H,d,J=8.8Hz),
12.31(1H,s).

5 MS (FAB) m/z: 622(M+H)⁺.

[Example 216]

N-{(1R,2S,5S)-2-[[(3-Chloro-5-fluoroindol-2-yl)carbonyl]-
amino]-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
10 hydrochloride:



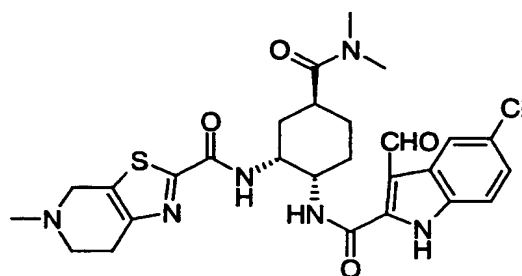
The title compound was obtained from the compound
obtained in Referential Example 253 and the compound
obtained in Referential Example 284 in a similar manner to
15 the process described in Example 5.

¹H-NMR (DMSO-d₆) δ: 1.40-1.51(1H,m), 1.75-2.00(5H,m),
2.79(3H,s), 2.92(3H,s), 2.99(3H,s), 3.10-3.21(3H,m), 3.29-
3.41(4H,m), 4.11-4.21(1H,m), 4.62-4.75(1H,m),
7.14(1H,dt,J=8.8,2.4Hz), 7.24(1H,dd,J=8.8,2.4Hz),
20 7.45(1H,dd,J=8.8,4.4Hz), 7.69(1H,d,J=2.5Hz),
8.79(1H,d,J=2.5Hz), 12.10(1H,s).

MS (FAB) m/z: 561(M+H)⁺.

[Example 217]

N-((1R,2S,5S)-2-(((5-Chloro-3-formylindol-2-yl)carbonyl)-amino)-5-((dimethylamino)carbonyl)cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
5 hydrochloride:



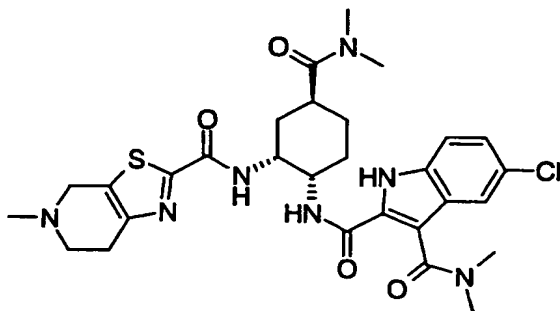
The title compound was obtained from the compound
obtained in Referential Example 253 and the compound
obtained in Referential Example 286 in a similar manner to
the process described in Example 5.
¹H-NMR (DMSO-d₆) δ: 1.40-1.51(1H,m), 1.75-1.89(4H,m), 1.90-
2.01(1H,m), 2.80(3H,s), 2.91(3H,s), 3.03(3H,s), 3.05-
3.33(3H,m), 3.60-3.71(1H,m), 4.11-4.21(1H,m), 4.32-
4.44(1H,m), 4.62-4.75(2H,m), 7.35(1H,dd,J=8.0,1.4Hz),
7.56(1H,d,J=8.0Hz), 8.21(1H,d,J=1.4Hz), 8.65(1H,t,J=7.4Hz),
9.92(1H,d,J=6.8Hz), 10.15(1H,t,J=9.1Hz),
13.00(1H,dt,J=6.4).

MS (FAB) m/z: 571(M+H)⁺.

[Example 218]

5-Chloro-N²-((1S,2R,4S)-4-((dimethylamino)carbonyl)-2-(((5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl)amino)cyclohexyl)-N³,N³-dimethylindole-2,3-

dicarboxamide hydrochloride:



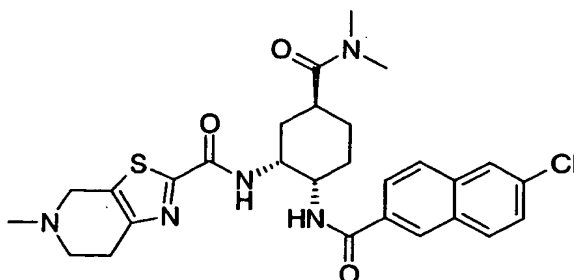
The title compound was obtained from the compound
obtained in Referential Example 253 and the compound
5 obtained in Referential Example 289 in a similar manner to
the process described in Example 5.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.40-1.51(1H,m), 1.75-2.01(5H,m),
2.78(9H,s), 2.93(3H,s), 3.01(3H,s), 3.10-3.33(3H,m), 3.40-
3.50(1H,m), 3.65-3.75(1H,m), 4.01-4.09(1H,m), 4.32-
10 4.44(1H,m), 4.62-4.75(2H,m), 7.25(1H,d,J=8.0Hz), 7.40-
7.50(2H,m), 8.62(1H,br), 9.08(1H,br), 12.28(1H,br).

MS (FAB) m/z : 614 ($M+H$) $^+$.

[Example 219]

N-{(1R,2S,5S)-2-[(6-Chloro-2-naphthoyl)amino]-5-
15 [(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
hydrochloride:



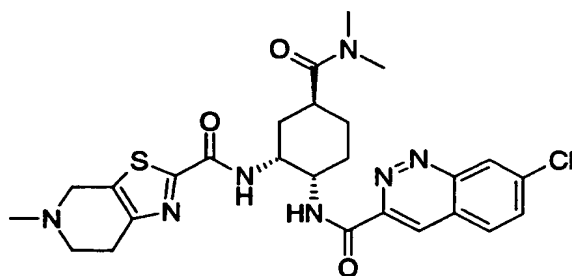
The compound (270 mg) obtained in Referential Example 294 was dissolved in methylene chloride (10 ml), and a 1N ethanol solution (10 ml) of hydrochloric acid was added to stir the mixture for 90 minutes. The solvent was distilled off under reduced pressure, and the resultant residue was dissolved in N,N-dimethylformamide (7 ml). The compound (110 mg) obtained in Referential Example 10, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg) and 1-hydroxybenzotriazole monohydrate (70 mg) were added to stir the mixture at room temperature for 23 hours. The reaction mixture was concentrated under reduced pressure, and water was added to conduct extraction with ethyl acetate. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified twice by column chromatography on silica gel (methylene chloride: methanol = 20:1 → 10:1). The thus-obtained free base was dissolved in methanol, and a 1N ethanol solution (0.30 ml) of hydrochloric acid was added. The residue was washed with ethyl acetate to obtain the title compound (130 mg).

¹H-NMR (DMSO-d₆) δ: 1.45-1.60 (1H,m), 1.70-1.90 (3H,m), 1.90-2.10 (2H,m), 2.81 (3H,s), 2.91 (3H,s), 3.00 (3H,s), 3.00-3.22 (3H,m), 3.53 (2H,br), 4.10-4.20 (1H,m), 4.30-4.70 (3H,m), 7.59 (1H,dd,J=8.8,2.2Hz), 7.87 (1H,d,J=8.5Hz), 7.96 (1H,d,J=8.5Hz), 8.02 (1H,d,J=8.8Hz), 8.10 (1H,d,J=2.2Hz), 8.33 (1H,s), 8.43 (1H,d,J=8.1Hz), 8.52 (1H,d,J=7.3Hz).

MS (FAB) m/z: 554 (M+H)⁺.

[Example 220]

7-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-carbonyl]amino)cyclohexyl)cinnoline-3-carboxamide hydrochloride:



The title compound was obtained by treating the compound obtained in Referential Example 299 with an ethanol solution of hydrochloric acid and then condensing it with the compound obtained in Referential Example 10 in a similar manner to the process described in Example 219.

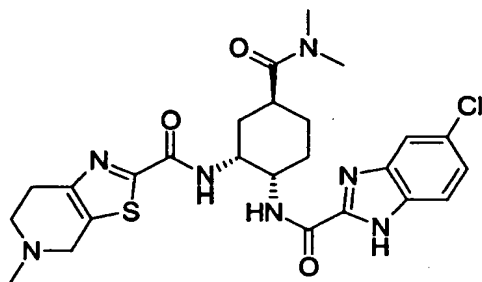
¹H-NMR (CDCl₃) δ: 1.50-1.65 (1H,m), 1.70-1.90 (3H,m), 2.05-2.15 (1H,m), 2.15-2.30 (1H,m), 2.81 (3H,s), 2.85-3.05 (8H,m), 3.15-3.25 (2H,m), 3.40-3.80 (1H,m), 4.25-4.80 (4H,m), 8.02 (1H,dd,J=8.8,2.0Hz), 8.38 (1H,d,J=8.8Hz), 8.66 (1H,s),

8.91(1H,s), 8.96(1H,d,J=7.3Hz), 9.53(1H,br).

MS (FAB) m/z: 556(M+H)⁺.

[Example 221]

N-((1R,2S,5S)-2-[[(5-Chlorobenzimidazol-2-yl)carbonyl]amino]-5-[(dimethylamino)carbonyl]cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained by treating the compound obtained in Referential Example 300 with an ethanol solution of hydrochloric acid and then condensing it with the compound obtained in Referential Example 10 in a similar manner to the process described in Example 219.

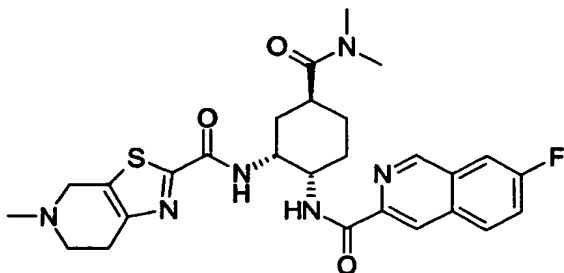
¹H-NMR (DMSO-d₆) δ: 1.45-1.60(1H,m), 1.60-1.83(3H,m), 2.00-2.20(2H,m), 2.78(3H,s), 2.92(6H,s), 3.00-3.30(3H,m), 3.47(2H,br.s), 4.10-4.75(4H,m), 7.30(1H,d,J=8.8Hz), 7.62(1H,d,J=12.5Hz), 7.63(1H,s), 8.75-8.87(1H,m), 9.09(1H,dd,J=12.5,8.8Hz), 11.20-11.40(1H,m).

MS (FAB) m/z: 546(M+H)⁺.

[Example 222]

N-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]amino)cyclohexyl)-7-fluoroisoquinoline-3-carboxamide hydrochloride:



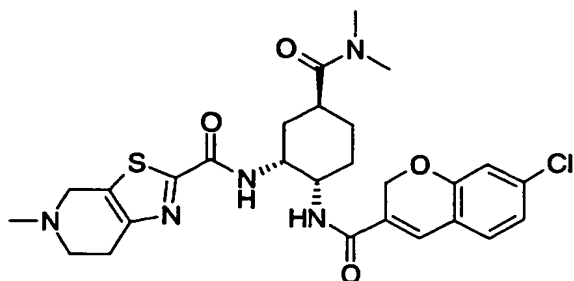
The title compound was obtained from the compound
 5 obtained in Referential Example 253 and the compound
 obtained in Referential Example 304 in a similar manner to
 the process described in Example 5.

¹H-NMR (DMSO-d₆) δ: 1.50-1.60 (1H,m), 1.70-1.85 (3H,m), 1.95-
 2.05 (1H,m), 2.10-2.20 (1H,m), 2.80 (3H,s), 2.90-3.90 (5H,m),
 10 2.93 (3H,s), 2.96 (3H,s), 4.10-4.75 (4H,m), 7.75-7.85 (1H,m),
 8.00-8.05 (1H,m), 8.30-8.35 (1H,m), 8.61 (1H,s),
 8.93 (2H,d,J=7.3Hz), 9.31 (1H,s).

MS (FAB) m/z: 539 (M+H)⁺.

[Example 223]

15 N-((1R,2S,5S)-2-(((7-chloro-2H-chromen-3-yl)carbonyl)-
 amino)-5-((dimethylamino)carbonyl)cyclohexyl)-5-methyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
 hydrochloride:



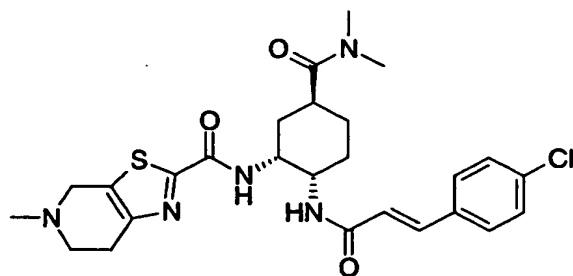
The compound (220 mg) obtained in Referential Example 252 was dissolved in methanol (10 ml), and 10% palladium on carbon (180 mg) was added to stir the mixture at room temperature for 4 hours in a hydrogen atmosphere. After the reaction mixture was filtered, the filtrate was concentrated under reduced pressure, and the residue was dissolved in N,N-dimethylformamide (30 ml). The compound (108 mg) obtained in Referential Example 306, 1-hydroxybenzotriazole monohydrate (78 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (196 mg) were added to stir the mixture at room temperature for a night. The reaction mixture was concentrated under reduced pressure, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 100:3) to obtain a pale yellow foamy substance. This foamy substance was dissolved in methylene

chloride (2 ml), a 1N ethanol solution (363 μ l) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. Diethyl ether was added to the residue. Precipitate formed was collected by filtration to
5 obtain the title compound (175 mg).

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.40-1.52(1H,m), 1.55-1.96(5H,m), 2.78(3H,s), 2.90(3H,s), 2.98(3H,s), 3.01-3.12(1H,m), 3.13-3.28(2H,m), 3.40-3.85(2H,m), 3.92-4.00(1H,m), 4.35-4.80(3H,m), 4.84(1H,d,J=14.5Hz), 4.89(1H,d,J=14.5Hz),
10 6.92(1H,s), 6.98(1H,dd,J=8.1,1.7Hz), 7.08(1H,s), 7.17(1H,d,J=8.3Hz), 8.12(1H,d,J=8.1Hz), 8.34(1H,d,J=8.1Hz).
MS (FAB) m/z : 558(M+H) $^+$.

[Example 224]

N-{(1R,2S,5S)-2-{[(E)-3(4-Chlorophenyl)-2-propenoyl]-
15 amino}-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
hydrochloride:



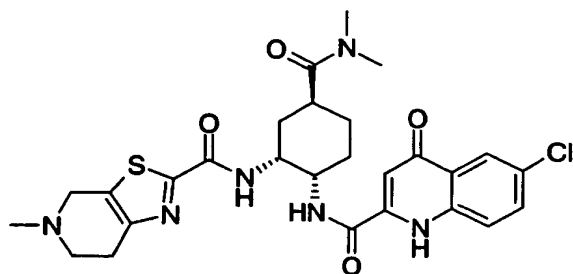
The title compound was obtained by treating the
20 compound obtained in Referential Example 307 with an ethanol solution of hydrochloric acid and then condensing it with the compound obtained in Referential Example 10 in

a similar manner to the process described in Example 219.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.35-1.55 (1H,m), 1.55-1.90 (4H,m),
2.79 (3H,s), 2.92 (3H,s), 2.99 (3H,s), 3.05-3.30 (3H,m), 3.40-
3.55 (1H,m), 3.60-3.75 (1H,m), 3.93-4.03 (2H,m), 4.35-
5 4.50 (1H,m), 4.50-4.60 (1H,m), 4.60-4.75 (1H,m),
6.65 (1H,d, $J=15.7$ Hz), 7.35 (1H,d, $J=15.7$ Hz),
7.44 (1H,d, $J=8.6$ Hz), 7.55 (1H,d, $J=8.6$ Hz),
8.03 (1H,d, $J=8.1$ Hz), 8.34 (1H,br.s), 11.25-11.70 (1H,br).
MS (ESI) m/z : 530 ($\text{M}+\text{H}$) $^+$.

10 [Example 225]

6-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-carbonyl]amino)cyclohexyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide hydrochloride:



15

The title compound was obtained from the compound obtained in Referential Example 253 and the compound obtained in Referential Example 309 in a similar manner to the process described in Example 5.

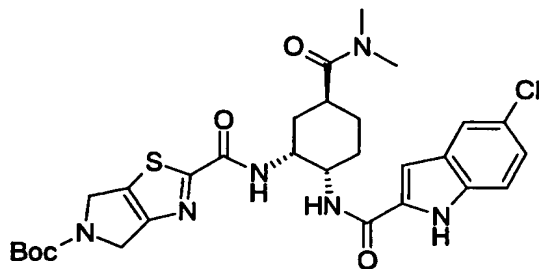
20 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.43-1.60 (1H,m), 1.65-2.10 (3H,m),
2.79 (3H,s), 2.92 (3H,s), 2.99 (3H,s), 3.05-3.20 (2H,m), 3.20-
3.80 (5H,m), 4.08-4.20 (1H,m), 4.35-4.50 (1H,m), 4.60-

4.70 (1H,m), 4.70 (1H,d,J=15.6Hz), 6.77 (1H,br.s),
7.73 (1H,d,J=8.9Hz), 7.94 (1H,d,J=8.9Hz), 7.97 (1H,d,J=2.2Hz),
8.54 (1H,br.s), 8.80-9.00 (1H,m), 11.70-12.50 (1H,br), 11.70-
12.50 (1H,br).

5 MS (ESI) m/z: 571 (M+H)⁺.

[Example 226]

tert-Butyl 2-[(1R,2S,5S)-2-[(5-chloroindol-2-yl)-
carbonyl]amino]-5-[(dimethylamino)carbonyl]cyclohexyl)-
amino)carbonyl]-4,6-dihydro-5H-pyrrolo[3,4-d]thiazole-5-
10 carboxylate:



1) The compound (1.46 g) obtained in Referential
Example 310 was dissolved in methylene chloride (10 ml),
and an ethanol solution (10 ml) of hydrochloric acid was
15 added at room temperature to stir the mixture for 1 hour.
After completion of the reaction, the solvent was
distilled off, ethanol was added, the mixture was
concentrated, and diisopropyl ether was added to the
residue to solidify it. The resultant solids were
20 collected by filtration to obtain N-[(1S,2R,4S)-2-amino-4-
[(dimethylamino)carbonyl]cyclohexyl)-5-chloroindole-2-
carboxamide hydrochloride.

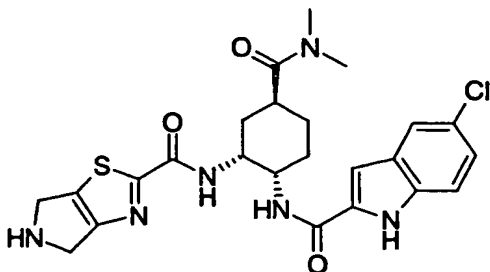
2) This product was dissolved in N,N-dimethylformamide (5 ml), and the compound (1.31 g) obtained in Referential Example 406, 1-hydroxybenzotriazole monohydrate (640 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.36 g) were added to stir the mixture at room temperature for 3 days. The reaction mixture was concentrated, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 1:19) to obtain the title compound (1.22 g).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.53(9H,s), 1.70-2.40(6H,m), 2.80-3.20(7H,m), 4.15-4.25(1H,m), 4.55-4.80(5H,m), 6.83(1H,d,J=1.5Hz), 7.20(1H,dd,J=8.8,2.0Hz), 7.33(1H,d,J=8.8Hz), 7.40-7.50(1H,m), 7.61(1H,br.s), 7.72-7.80(1H,m), 9.41(1H,br.s).

MS (ESI) m/z: 615(M+H) $^+$.

[Example 227]

5-Chloro-N-{(1S,2R,4S)-2-[[(5,6-dihydro-4H-pyrrolo[3,4-d]-thiazol-2-yl)carbonyl]amino]-4-[(dimethylamino)carbonyl]-cyclohexyl}indole-2-carboxamide hydrochloride:



The compound (1.22 g) obtained in Referential Example 226 was dissolved in methylene chloride (5 ml), and an ethanol solution (10 ml) of hydrochloric acid was added to stir the mixture for 1 hour. After the reaction mixture was concentrated, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to conduct liquid separation, and the resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 1:9) to obtain a free base (636 mg) of the title compound as a colorless glassy solid. The free base (200 mg) was dissolved in a 1N ethanol solution (1 ml) of hydrochloric acid. After the solution was concentrated, ethyl acetate was added to solidfy the residue. The thus-obtained colorless powder was collected by filtration and dried to obtain the title compound (195 mg).

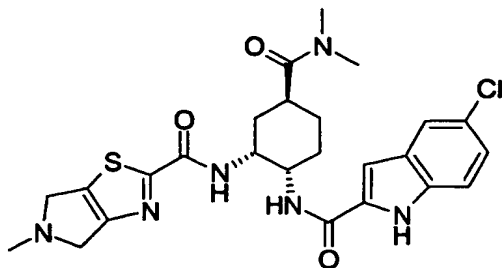
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.45-1.60 (1H,m), 1.70-1.90 (3H,m), 1.90-2.05 (2H,m), 2.80 (3H,s), 2.98 (3H,s), 2.98-3.15 (1H,m), 4.05-4.20 (1H,m), 4.44 (2H,br.s), 4.58 (3H,br.s), 7.05 (1H,d,J=1.5Hz), 7.16 (1H,dd, J=8.7,1.8Hz),

7.42 (1H, d, J=8.7Hz), 7.68 (1H, d, J=1.8Hz), 8.38 (1H, d, J=7.8Hz),
8.42 (1H, d, J=7.8Hz), 10.45-10.65 (2H, br), 11.78 (1H, br.s).

MS (FAB) m/z: 515 (M+H)⁺.

[Example 228]

- 5 5-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)carbonyl]amino)cyclohexyl)indole-2-carboxamide hydrochloride:



- 10 The title compound was obtained from the compound obtained in Example 227 and formalin in a similar manner to the process described in Example 18.

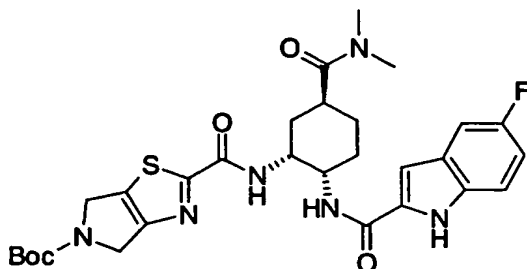
- ¹H-NMR (DMSO-d₆) δ: 1.45-1.60 (1H, m), 1.65-1.90 (3H, m), 1.90-2.05 (2H, m), 2.80 (3H, s), 2.98 (3H, s), 2.98-3.06 (1H, m),
15 3.06 (3H, s), 4.05-4.20 (1H, m), 4.30-5.00 (5H, br.s),
7.04 (1H, d, J=1.7Hz), 7.17 (1H, dd, J=8.8, 2.1Hz)
, 7.41 (1H, d, J=8.8Hz) 7.68 (1H, d, J=2.1Hz) 8.36 (1H, d, J=7.8Hz),
8.42 (1H, d, J=8.1Hz), 11.78 (1H, br.s), 12.14 (1H, br.s).

MS (FAB) m/z: 529 (M+H)⁺.

- 20 [Example 229]

tert-Butyl 2-[[[(1R,2S,5S)-5-[(dimethylamino)carbonyl]-2-[[5-fluoroindol-2-yl)carbonyl]amino]cyclohexyl)amino]-

carbonyl}-4,6-dihydro-5H-pyrrolo[3,4-d]thiazole-5-carboxylate:



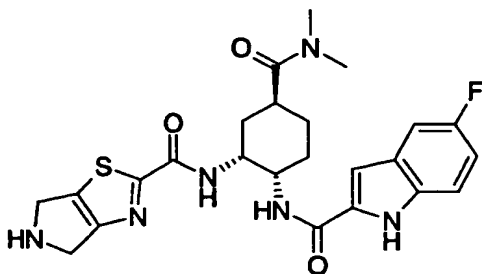
The title compound was obtained from the compound
 5 obtained in Referential Example 311 and the compound
 obtained in Referential Example 406 in a similar manner to
 the process described in Example 226.

¹H-NMR (CDCl₃) δ: 1.53(9H,s), 1.60-2.40(6H,m), 2.80-
 3.20(7H,m), 4.15-4.25(1H,m), 4.55-4.80(5H,m), 6.84-
 10 6.87(1H,m), 7.01(1H,dt, J=2.4, 9.1Hz), 7.25-7.30(1H,m),
 7.34(1H,dd, J=9.1, 4.3Hz), 7.42-7.49(1H,m), 7.70-7.80(1H,m),
 9.37-9.45(1H,m).

MS (ESI) m/z: 599(M+H)⁺.

[Example 230]

15 N-{(1S,2R,4S)-2-[[(5,6-Dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)carbonyl]amino]-4-[(dimethylamino)carbonyl]-5-fluoroindole-2-carboxamide hydrochloride:



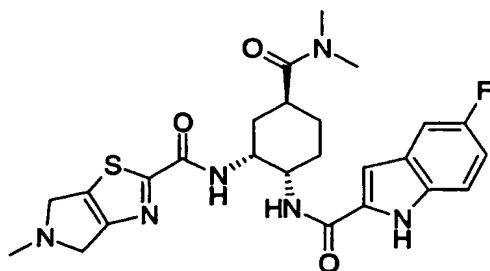
The title compound was obtained from the compound obtained in Example 229 in a similar manner to the process described in Example 227.

¹H-NMR (DMSO-d₆) δ: 1.45-1.60 (1H,m), 1.65-1.90 (3H,m), 1.90-2.10 (2H,m), 2.80 (3H,s), 2.97 (3H,s), 2.98-3.15 (1H,m), 4.05-4.20 (1H,m), 4.35-4.50 (2H,m), 4.58 (3H,br.s), 6.97-7.10 (2H,m), 7.35-7.47 (2H,m), 8.34 (1H,d,J=7.8Hz), 8.41 (1H,d,J=8.1Hz), 10.53 (2H,br.s), 11.68 (1H,br.s).

MS (FAB) m/z: 499 (M+H)⁺.

[Example 231]

N-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-[[(5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)carbonyl]amino]-cyclohexyl)-5-fluoroindole-2-carboxamide hydrochloride:



15

The title compound was obtained from the compound obtained in Example 230 and formalin in a similar manner

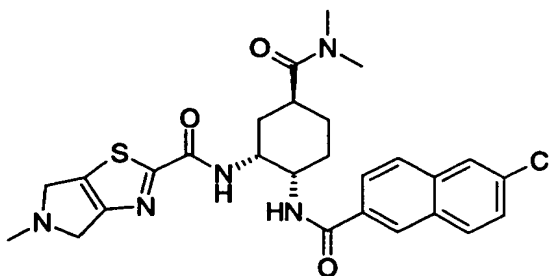
to the process described in Example 18.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.45-1.60 (1H, m), 1.65-1.90 (3H, m), 1.90-2.10 (2H, m), 2.80 (3H, s), 2.90-3.20 (7H, m), 4.05-4.20 (1H, m), 4.30-5.00 (5H, br. s), 6.95-7.10 (2H, m), 7.35-7.50 (2H, m),
5 8.33 (1H, d, $J=7.6\text{Hz}$), 8.41 (1H, d, $J=8.1\text{Hz}$), 11.67 (1H, br. s), 12.37 (1H, br. s).

MS (FAB) m/z : 513 ($\text{M}+\text{H}$) $^+$.

[Example 232]

N-((1R,2S,5S)-2-[(6-Chloro-2-naphthoyl)amino]-5-
10 [(dimethylamino)carbonyl]cyclohexyl)-5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazole-2-carboxamide hydrochloride:



The title compound was obtained from the compound
obtained in Referential Example 294 and the compound
15 obtained in Referential Example 293 in a similar manner to the process described in Example 226.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.48-1.56 (1H, m), 1.71-1.84 (3H, m), 1.95-2.04 (2H, m), 2.81 (3H, s), 3.00 (3H, s), 3.02 (3H, s), 3.06-3.15 (2H, m), 4.13-4.14 (1H, m), 4.52-4.63 (4H, m),
20 7.60 (1H, d, $J=8.5\text{Hz}$), 7.87 (1H, d, $J=8.8\text{Hz}$), 7.96 (1H, d, $J=8.5\text{Hz}$), 8.01 (1H, d, $J=8.8\text{Hz}$), 8.10 (1H, s), 8.32 (1H, s), 8.45 (1H, d, $J=8.1\text{Hz}$), 8.51 (1H, d, $J=7.3\text{Hz}$).

MS (FAB) m/z: 540 (M+H)⁺.

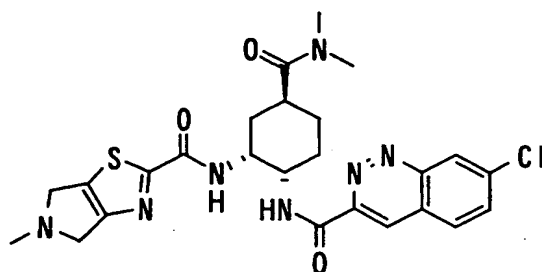
[Example 233]

7-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-

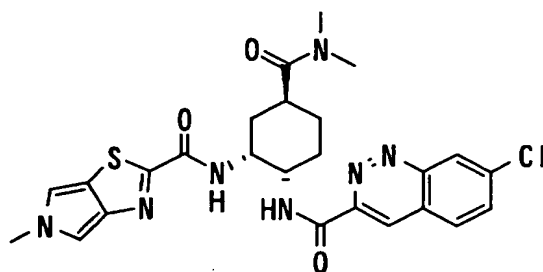
5 carbonyl]amino)cyclohexyl)cinnoline-3-carboxamide

hydrochloride and 7-chloro-N-((1S,2R,4S)-4-

[(dimethylamino)carbonyl]-2-[[5-methyl-5H-pyrrolo[3,4-d]thiazol-2-yl)carbonyl]amino)cyclohexyl)cinnoline-3-carboxamide:



10



15

A 4N dioxane solution (3.0 ml) of hydrochloric acid was added to a suspension of the compound (330 mg) obtained in Referential Example 299 in a mixed solvent of dioxane (3.0 ml) and methylene chloride (3.0 ml), and the mixture was stirred at room temperature for 30 minutes. The solvent was distilled off under reduced pressure, and

the thus-obtained white powder was dissolved in N,N-dimethylformamide (5.0 ml), and the compound (172 mg) obtained in Referential Example 293, 1-hydroxybenzotriazole monohydrate (130 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (192 mg) were added to stir the mixture at room temperature for 15 hours. The solvent was distilled off under reduced pressure, methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue. The resultant organic layer was washed with saturated saline and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1). A 1N ethanol solution (0.35 ml) of hydrochloric acid was added to a solution of the thus-obtained high-polar compound mainly formed in ethanol (4.0 ml), and the solvent was distilled off under reduced pressure. Ethanol and diethyl ether were added to the residue, and precipitate formed was collected by filtration to obtain 7-chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)carbonyl]amino)cyclohexyl)cinnoline-3-carboxamide hydrochloride (184 mg) a main product.

¹H-NMR (DMSO-d₆) δ: 1.50-1.65(1H,m), 1.70-1.90(3H,m), 2.03-2.12(1H, m), 2.15-2.30(1H,m), 2.81(3H,s), 2.90-3.05(1H,m), 2.96(3H,s), 3.07(3H,s), 4.28-4.37(1H, m); 4.40-4.95(5H,br),

8.02 (1H, d, J=8.8Hz), 8.38 (1H, d, J=8.8Hz), 8.66 (1H, s),
8.91 (1H, s), 8.97 (1H, d, J=7.1Hz), 9.43-9.57 (1H, br), 11.75-
11.95 (0.5H, br), 12.35-11.55 (0.5H, br).

MS (FAB) m/z: 542 (M+H)⁺.

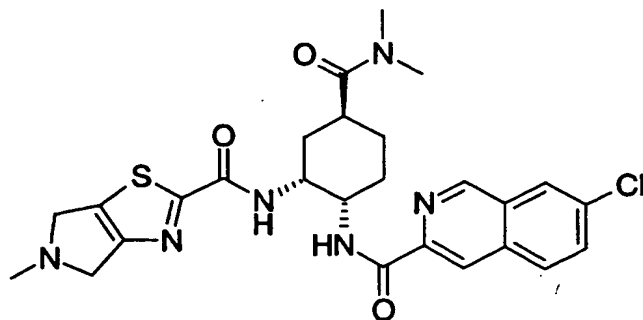
5 In the purification by the column chromatography on
silica gel, low-polar 7-chloro-N-((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[(5-methyl-5H-pyrrolo[3,4-
d]thiazol-2-yl)carbonyl]amino)cyclohexyl)cinnoline-3-
carboxamide (98 mg) was also obtained as a by-product.

10 ¹H-NMR (CDCl₃) δ: 1.90-2.25 (6H, m), 2.85-3.00 (1H, m),
2.95 (3H, s), 3.05 (3H, s), 3.91 (3H, s), 4.43-4.54 (1H, m),
4.86-4.95 (1H, m), 6.70 (1H, d, J=1.5Hz), 7.19 (1H, d, J=1.5Hz),
7.59 (1H, d, J=8.8Hz), 7.76 (1H, d, J=8.8Hz), 7.95 (1H, d, J=8.8Hz),
8.53 (1H, s), 8.64 (1H, d, J=8.0Hz), 8.73 (1H, s).

15 MS (FAB) m/z: 540 (M+H)⁺.

[Example 234]

7-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[(5-
methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-
carbonyl]amino)cyclohexyl)isoquinoline-3-carboxamide
20 hydrochloride



The compound (500 mg) obtained in Referential Example 146 was dissolved in an ethanol solution (5 ml) of hydrochloric acid, and the mixture was stirred at room temperature for 30 minutes. The solvent was distilled off under reduced pressure, and the residue was dissolved in N,N-dimethylformamide (7 ml), and the compound (299 mg) obtained in Referential Example 293, 1-hydroxy-benzotriazole monohydrate (71 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (403 mg) were added to the solution to stir the mixture at room temperature for a night. The solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation. The resultant water layer was extracted with methylene chloride. Organic layers were combined and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 93:7) to obtain a free base (260 mg) of the title compound as a pale yellow solid. This product was dissolved in methylene chloride, a 1N ethanol solution (961 μ l) of hydrochloric acid was added, and the solvent was distilled off under reduced pressure. A small amount of methanol was added to the residue, and diethyl ether was added dropwise to collect precipitate formed by filtration. This product was washed with diethyl ether to

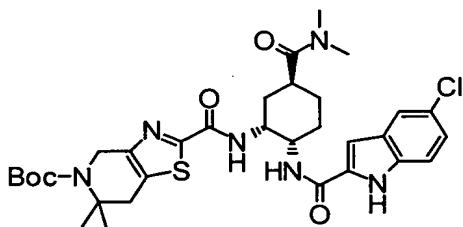
obtain the title compound (260 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.47-1.56 (1H, m), 1.71-1.75 (3H, m),
1.95-1.99 (1H, m), 2.12-2.15 (1H, m), 2.78 (3H, s), 2.95 (3H, s),
2.98 (1H, br. s), 3.05 (3H, s), 4.19-4.22 (1H, m), 4.44-4.52 (3H, m),
5 4.74-4.88 (2H, m), 7.87 (1H, dd, $J=8.8, 1.7\text{Hz}$), 8.24 (1H, d, $J=8.8\text{Hz}$),
8.36 (1H, d, $J=1.7\text{Hz}$), 8.58 (1H, s), 8.90-8.92 (2H, m), 9.30 (1H, s),
12.65-12.75 (1H, m).

MS (FAB) m/z : 541 ($\text{M}+\text{H}$) $^+$.

[Example 235]

10 tert-Butyl 2-[(1R,2S,5S)-2-[(5-chloroindol-2-yl)-
carbonyl]amino]-5-[(dimethylamino)carbonyl]cyclohexyl)-
amino)carbonyl]-6,6-dimethyl-6,7-dihydrothiazolo[4,5-
c]pyridine-5(4H)-carboxylate:



15 The compound (95.4 mg) obtained in Referential
Example 316 was dissolved in diethyl ether (1 ml) in an
argon atmosphere, and tert-butyllithium (1.60N pentane
solution, 244 μl) was added dropwise at -78°C . After the
mixture was stirred for 1 hour at -78°C , carbon dioxide was
20 blown into the reaction mixture for 10 minutes. The
reaction mixture was heated to room temperature. After the
reaction mixture was concentrated under reduced pressure,
the residue was dissolved in N,N-dimethylformamide (5 ml).

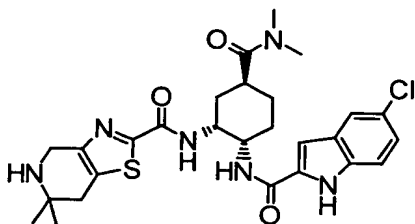
To the solution, were successively added the compound (178 mg) obtained in Referential Example 432 , 1-hydroxybenzotriazole monohydrate (48.0 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (136 mg). The resultant mixture was stirred overnight at room temperature. The reaction mixture was concentrated, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (methanol:methylene chloride = 1:19) to obtain the title compound (140 mg).

¹H-NMR (CDCl₃) δ: 1.50 (9H, s), 1.52 (3H, s), 1.54 (3H, s), 1.70-2.10 (4H, m), 2.15-2.45 (2H, m), 2.80-3.20 (9H, m), 4.10-4.25 (1H, br), 4.60-4.75 (3H, m), 6.85 (1H, br. s), 7.21 (1H, dd, J=8.8, 1.8 Hz), 7.34 (1H, d, J=8.8 Hz), 7.48 (1H, d, J=7.3 Hz), 7.61-7.63 (1H, m), 7.89 (1H, br. s), 9.27 (1H, br. s).

MS (ESI) m/z: 657 (M+H)⁺.

[Example 236]

N-((1R,2S,5S)-2-([(5-Chloroindol-2-yl)carbonyl]amino)-5-[(dimethylamino)carbonyl]cyclohexyl)-6,6-dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine-2-carboxamide hydrochloride:



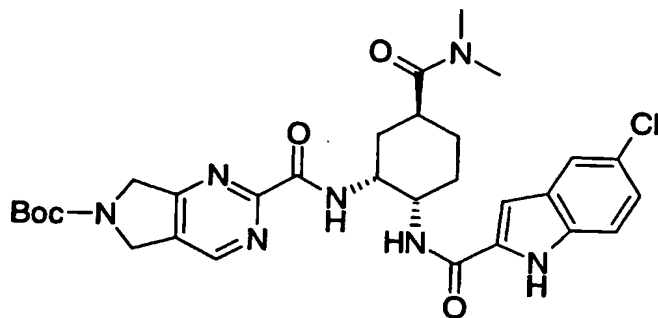
The title compound was obtained from the compound obtained in Example 235 in a similar manner to the process described in Example 227.

- 5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.40 (6H, s), 1.45-1.60 (1H, m),
 1.70-2.05 (5H, m), 2.81 (3H, s), 2.95-3.15 (6H, m),
 4.05-4.20 (1H, br), 4.25-4.45 (2H, m), 4.55-4.65 (1H, m),
 7.06 (1H, d, $J=1.7\text{Hz}$), 7.17 (1H, dd, $J=8.8, 2.0\text{Hz}$),
 7.42 (1H, d, $J=8.8\text{Hz}$), 7.68 (1H, d, $J=2.0\text{Hz}$), 8.34-8.39 (2H, m),
 10 9.77 (1H, br. s), 9.84 (1H, br. s), 11.79 (1H, br. s).

MS (ESI) m/z : 557 ($\text{M}+\text{H}$) $^+$.

[Example 237]

tert-Butyl 2-[(1R,2S,5S)-2-[(5-chloroindol-2-yl)-
 carbonyl]amino]-5-[(dimethylamino)carbonyl]cyclohexyl]-
 15 amino)carbonyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-
 carboxylate:



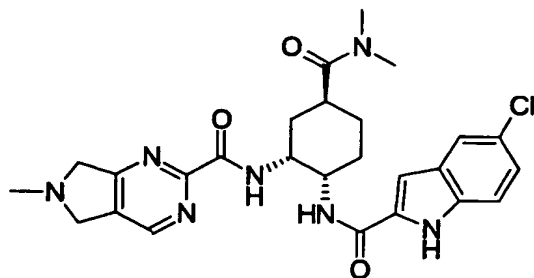
The compound (1.27 g) obtained in Referential Example 50 was dissolved in tetrahydrofuran (48 ml), and lithium hydroxide (117 mg) and water (6.0 ml) were added to stir the mixture at room temperature for 4.5 hours. The reaction mixture was dried to solid under reduced pressure to obtain a crude carboxylic acid lithium salt (1.24 g). This product was condensed with the compound obtained in Referential Example 432 in a similar manner to the process described in the step 2) of Example 226 to obtain the title compound.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.50-1.70 (1H, m), 1.54 (9H, s), 1.80-2.10 (3H, m), 2.25-2.50 (2H, m), 2.85-2.95 (1H, m), 2.99 (3H, s), 3.14 (3H, s), 4.15-4.25 (1H, m), 4.65-4.75 (1H, m), 4.80-4.90 (4H, m), 6.97 (1H, s), 7.15-7.25 (1H, m), 7.30-7.40 (1H, m), 7.60-7.65 (1H, m), 8.15-8.25 (1H, m), 8.40-8.45 (1H, m), 8.75-8.85 (1H, m), 9.40-9.45 (1H, m).

MS (ESI) m/z : 611 ($M+H$) $^+$.

[Example 238]

N-{(1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl)-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidine-2-carboxamide hydrochloride:



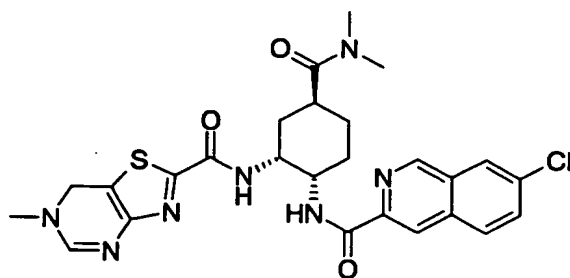
The compound (367 mg) obtained in Example 237 was dissolved in methylene chloride (10 ml), and trifluoroacetic acid (10 ml) was added to stir the mixture at room temperature for 2 hours. The reaction mixture was dried to solid under reduced pressure. The title compound was obtained from the thus-obtained crude product and formalin in a similar manner to the process described in Example 18.

¹H-NMR (DMSO-d₆) δ: 1.50-1.60 (1H, m), 1.65-2.10 (5H, m), 2.81 (3H, s), 2.90-3.00 (1H, m), 2.96 (3H, s), 3.05 (3H, s), 4.10-4.20 (1H, m), 4.55-4.65 (1H, m), 4.65-4.90 (4H, br), 7.06 (1H, s), 7.15 (1H, dd, J=8.7, 2.1 Hz), 7.41 (1H, d, J=8.8 Hz), 7.66 (1H, d, J=1.7 Hz), 8.35-8.45 (1H, m), 8.57 (1H, d, J=8.1 Hz), 9.00 (1H, s), 11.80 (1H, s), 11.90-12.20 (1H, m).

MS (FAB) m/z: 524 (M+H)⁺.

[Example 239]

7-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[(6-methyl-6,7-dihydrothiazolo[4,5-d]pyrimidin-2-yl)-carbonyl]amino)cyclohexyl)isoquinoline-3-carboxamide hydrochloride

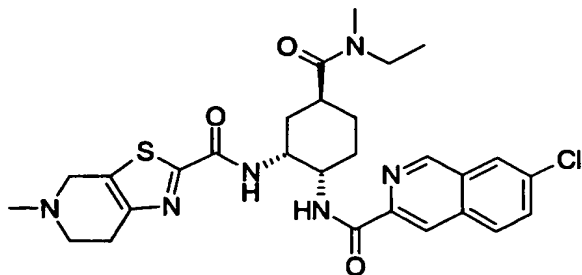


The title compound was obtained by treating the compound obtained in Referential Example 146 with an ethanol solution of hydrochloric acid and then condensing it with the compound obtained in Referential Example 322 in a similar manner to the process described in Example 49.

¹H-NMR (DMSO-d₆) δ: 1.50-1.60 (1H,m), 1.70-1.90 (3H,m), 1.90-2.15 (2H,m), 2.81 (3H,s), 2.95 (3H,s), 2.90-3.05 (1H,m), 3.26 (3H,s), 4.20-4.55 (2H,m), 5.00 (2H,s), 7.91 (1H,d,J=8.8Hz), 8.27 (1H,d,J=8.8Hz), 8.37 (1H,s), 8.54 (1H,s), 8.62 (1H,s), 8.79 (1H,d,J=8.3Hz), 8.94 (1H,d,J=8.1Hz), 9.32 (1H,s).
MS (ESI) m/z: 554 (M+H)⁺.

[Example 240]

7-Chloro-N-((1S,2R,4S)-4-{[ethyl(methyl)amino]carbonyl}-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino)cyclohexyl)isoquinoline-3-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 325 and the compound obtained in Referential Example 10 in a similar manner to the process described in Example 2.

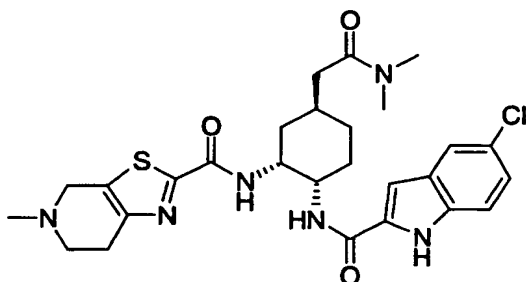
¹H-NMR (DMSO-d₆) δ: 0.98, 1.04 (3H,each t,J=7.1Hz),

1.52-1.60 (1H,m) , 1.74-1.77 (3H,m) , 1.96-2.05 (1H,m) ,
 2.15-2.18 (1H,m) , 2.77-2.93 (8H,m) , 3.17-3.32 (3H,m) ,
 3.49 (1H,br.s) , 4.22 (1H,br.s) , 4.41-4.45 (1H,m) ,
 4.51 (1H,br.s) , 4.69-4.72 (1H,m) , 7.89 (1H,d,J=8.7Hz) ,
 5 8.26 (1H,d,J=8.7Hz) , 8.37 (1H,s) , 8.60 (1H,s) , 8.91-8.98 (2H,m) ,
 9.32 (1H,d,J=6.6Hz) , 11.39, 11.53 (1H,each m) .

MS (FAB) m/z: 569 (M+H)⁺.

[Example 241]

N-((1R*,2S*,5S*)-2-((5-Chloroindol-2-yl)carbonyl)amino)-
 10 5-[2-(dimethylamino)-2-oxoethyl]cyclohexyl]-5-methyl-
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
 hydrochloride:



The title compound was obtained from the compound
 15 obtained in Referential Example 336 and the compound
 obtained in Referential Example 10 in a similar manner to
 the process described in Example 2.

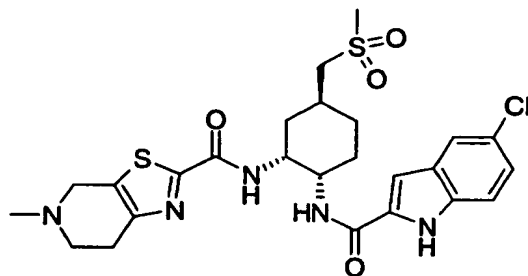
¹H-NMR (DMSO-d₆) δ: 1.13-1.22 (1H,m) , 1.40-1.46 (1H,m) ,
 1.68-1.99 (5H,m) , 2.18-2.29 (2H,m) , 2.80 (3H,s) , 2.92 (3H,s) ,
 20 2.96 (3H,s) , 3.22 (2H,br.s) , 3.49 (1H,br.s) , 3.70 (1H,br.s) ,
 4.09-4.16 (1H,m) , 4.42-4.46 (2H,m) , 4.67 (1H,br.s) , 7.03 (1H,s) ,
 7.16 (1H,dd,J=8.5,1.5Hz) , 7.42 (1H,d,J=8.5Hz) , 7.67 (1H,s) ,

8.01 (1H, d, J=8.5 Hz), 8.40 (1H, d, J=7.8 Hz), 11.35-11.58 (1H, m),
11.76 (1H, br. s).

MS (FAB) m/z: 557 (M+H)⁺.

[Example 242]

- 5 N-((1R,2S,5S)-2-((5-chloroindol-2-yl)carbonyl)amino)-5-
[(methylsulfonyl)methyl]cyclohexyl)-5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
hydrochloride:



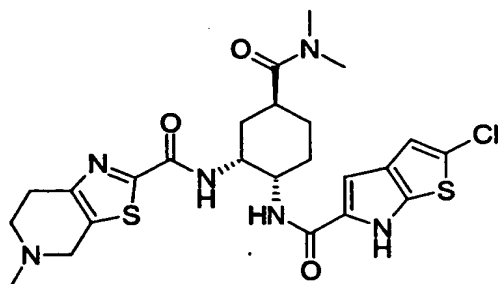
- 10 The title compound was obtained by treating the
compound obtained in Referential Example 340 with an
ethanol solution of hydrochloric acid and then condensing
it with the compound obtained in Referential Example 10 in
a similar manner to the process described in Example 219.

- 15 ¹H-NMR (DMSO-d₆) δ: 1.35-1.40 (1H, m), 1.55-1.62 (1H, m),
1.70-1.76 (1H, m), 1.88-1.94 (1H, m), 2.03-2.07 (1H, m),
2.13-2.17 (1H, m), 2.30-2.33 (1H, m), 2.43-3.48 (10H, m),
3.60-3.73 (2H, m), 4.11-4.16 (1H, m), 4.40-4.42 (2H, m),
4.68-4.73 (1H, m), 7.05 (1H, s), 7.16 (1H, dd, J=2.0, 8.8 Hz),
20 7.41 (1H, d, J=8.8 Hz), 7.68 (1H, s), 8.26 (1H, d, J=7.8 Hz),
8.39 (1H, d, J=7.8 Hz), 11.78 (1H, br. s).

MS (ESI) m/z: 564 (M+H)⁺.

[Example 243]

N-{(1R,2S,5S)-2-[[(2-Chloro-6H-thieno[2,3-b]pyrrol-5-yl) carbonyl] amino}-5-[(dimethylamino) carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



The title compound was obtained by hydrogenation of the compound obtained in Referential Example 252 and then condensing it with the compound obtained in Referential Example 345 in a similar manner to the process described in Example 223.

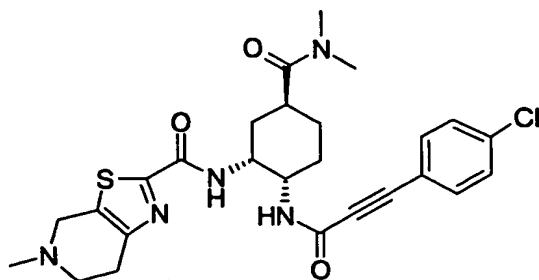
$^1\text{H-NMR}$ (CDCl_3) δ : 1.56-1.66 (1H, m), 1.76-1.93 (2H, m), 2.02-2.06 (1H, m), 2.19-2.26 (1H, m), 2.30-2.34 (1H, m), 2.52 (3H, s), 2.79-2.88 (3H, m), 2.91-2.94 (2H, m), 2.96 (3H, s), 3.09 (3H, s), 3.69-3.77 (2H, m), 4.13-4.19 (1H, m), 4.58-4.61 (1H, m), 6.72 (1H, s), 6.84 (1H, s), 7.50 (1H, d, $J=7.3\text{Hz}$), 7.60 (1H, d, $J=5.8\text{Hz}$), 10.54 (1H, br).

MS (ESI) m/z : 549 ($\text{M}+\text{H}$) $^+$.

[Example 244]

N-{(1R,2S,5S)-2-[[3-(4-Chlorophenyl)-2-propynoyl] amino}-5-[(dimethylamino) carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide

hydrochloride:



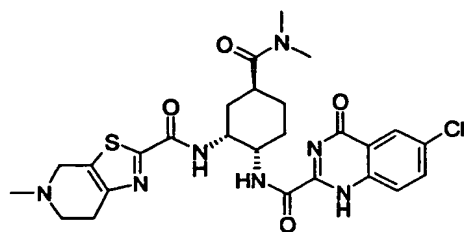
The title compound was obtained by hydrogenation of the compound obtained in Referential Example 252 and then
5 condensing it with the compound obtained in Referential Example 347 in a similar manner to the process described in Example 223.

$^1\text{H-NMR}$ (DMSO- d_6) δ : 1.38-1.50 (1H,m), 1.58-1.92 (4H,m),
2.78 (3H,s), 2.90 (3H,s), 2.97 (3H,s), 3.01-3.24 (3H,m),
10 3.26-3.80 (2H,m), 3.90-3.98 (1H,m), 4.30-4.78 (3H,m),
7.51 (1H,d,J=8.8Hz), 7.57 (1H,d,J=8.8Hz), 8.34 (1H,d,J=8.8Hz),
8.83 (1H,d,J=7.8Hz).

MS (FAB) m/z : 528 (M+H) $^+$.

[Example 245]

15 6-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-carbonyl]amino)cyclohexyl)-4-oxo-1,4-dihydroquinazoline-2-carboxamide hydrochloride:



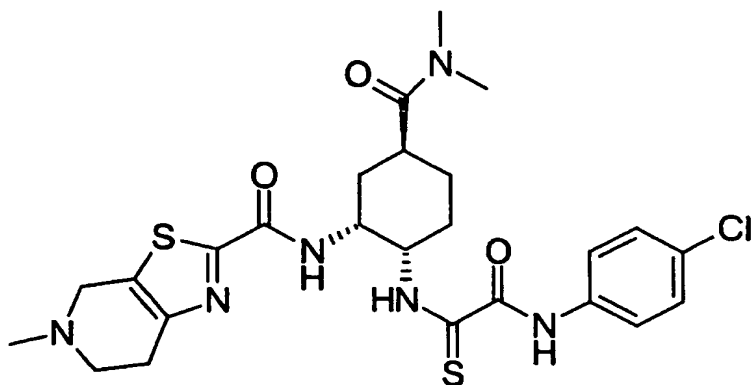
The title compound was obtained by hydrogenation of the compound obtained in Referential Example 252 and then condensing it with the compound obtained in Referential
 5 Example 349 in a similar manner to the process described in Example 223.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.45-1.60 (1H, m), 1.70-1.90 (3H, m),
 1.90-2.20 (3H, m), 2.80 (3H, s), 2.93 (3H, s), 2.97 (3H, s),
 2.98-3.80 (4H, m), 4.05-4.20 (2H, m), 4.35-4.80 (3H, m),
 10 7.63 (1H, d, $J=8.3\text{Hz}$), 7.90 (1H, d, $J=7.3\text{Hz}$), 8.75-9.00 (2H, m),
 11.00-11.50 (1H, br), 12.53 (1H, br. s).

MS (ESI) m/z : 573 ($\text{M}+\text{H}$) $^+$.

[Example 246]

N-{(1R,2S,5S)-2-{[2-(4-Chloroanilino)-2-oxoethane-
 15 thioyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



The compound (184 mg) obtained in Referential Example 253 and the compound (150 mg) obtained in Referential Example 351 were dissolved in a mixed solvent of methanol (1 ml)-methylene chloride (4 ml), the solution was heated and stirred at 150°C, and the heating was continued for 5 minutes after distilling off the solvent. After the reaction mixture was allowed to cool, the formed product was purified by column chromatography on silica gel (methylene chloride:methanol = 24:1) to obtain the title compound (59 mg).

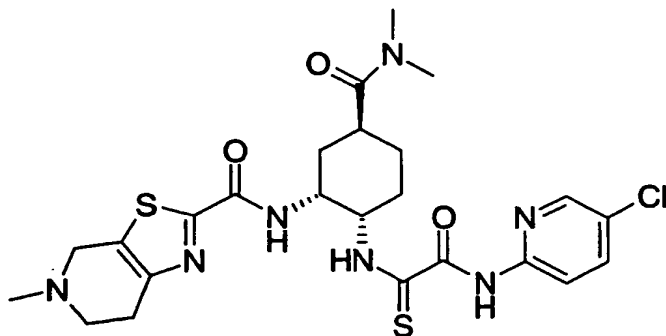
¹H-NMR (CDCl₃) δ: 1.65-1.90 (2H, m), 1.90-2.00 (1H, m), 2.00-2.15 (2H, m), 2.20-2.30 (1H, m), 2.52 (3H, s), 2.75-2.95 (5H, m), 2.96 (3H, s), 3.07 (3H, s), 3.68 (1H, d, J=15.2 Hz), 3.75 (1H, d, J=15.7 Hz), 4.45-4.60 (1H, m), 4.80-4.85 (1H, m), 7.31 (2H, d, J=8.8 Hz), 7.44 (1H, d, J=8.6 Hz), 7.60 (2H, d, J=8.8 Hz), 9.99 (1H, d, J=7.6 Hz), 10.15 (1H, s).

MS (ESI) m/z: 563 (M+H)⁺.

[Example 247]

N-((1R,2S,5S)-2-((2-[(5-Chloropyridin-2-yl)amino]-2-

oxoethanethioyl}amino)-5-[(dimethylamino)carbonyl]-
cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridine-2-carboxamide:

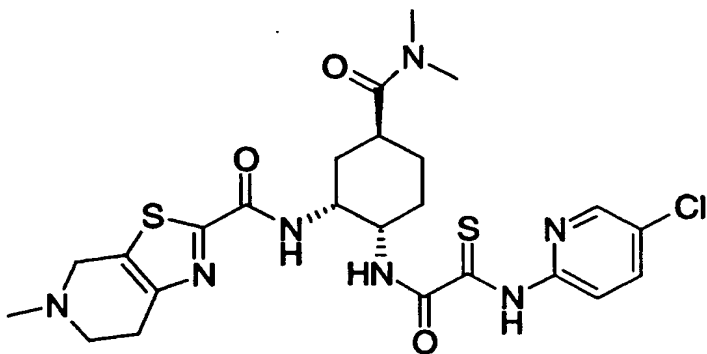


5 The compound (184 mg) obtained in Referential Example
253 and the compound (150 mg) obtained in Referential
Example 353 were dissolved in a mixed solvent of methanol
(0.3 ml)-methylene chloride (0.3 ml), the solution was
heated and stirred at 150°C, and the heating was continued
10 for 5 minutes after distilling off the solvent. reaction
mixture was allowed to cool, the formed product was
purified by column chromatography on silica gel (methylene
chloride:methanol = 24:1) to obtain the title compound (52
mg).

15 $^1\text{H-NMR}$ (CDCl_3) δ : 1.60-2.00 (3H, m), 2.00-2.20 (2H, m),
2.25-2.40 (1H, m), 2.53 (3H, s), 2.80-2.95 (5H, m), 2.96 (3H, s),
3.08 (3H, s), 3.70 (1H, d, $J=15.4\text{Hz}$), 3.75 (1H, d, $J=15.4\text{Hz}$),
4.45-4.60 (1H, m), 4.75-4.85 (1H, m), 7.45 (1H, d, $J=8.3\text{Hz}$),
7.67 (1H, dd, $J=8.8, 2.5\text{Hz}$), 8.18 (1H, d, $J=8.8\text{Hz}$),
20 8.31 (1H, d, $J=2.0\text{Hz}$), 10.06 (1H, d, $J=6.3\text{Hz}$), 10.56 (1H, s).
MS (ESI) m/z : 564 ($\text{M}+\text{H}$) $^+$.

[Example 248]

N-((1R,2S,5S)-2-((2-((5-Chloropyridin-2-yl)amino)-2-thioxoacetyl)amino)-5-((dimethylamino)carbonyl)-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:



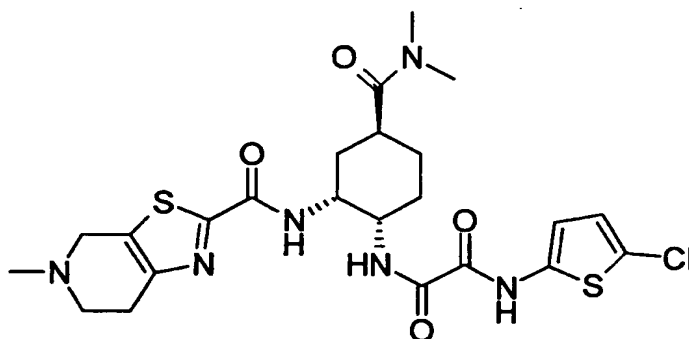
The compound (72 mg) obtained in Referential Example 355 and 2-amino-5-chloropyridine (100 mg) were dissolved in a mixed solvent of methanol (0.2 ml)-methylene chloride (0.2 ml), the solution was heated and stirred at 150°C, and the heating was continued for 8 minutes after distilling off the solvent. After the reaction mixture was allowed to cool, the formed product was purified by preparative thin-layer chromatography on silica gel (methylene chloride:methanol = 23:2) to obtain the title compound (4 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.60-2.00 (3H,m), 2.00-2.20 (3H,m), 2.53 (3H,s), 2.75-3.00 (5H,m), 2.95 (3H,s), 3.05 (3H,s), 3.65-3.80 (2H,m), 4.05-4.15 (1H,m), 4.70-4.80 (1H,m), 7.28 (1H,d),

7.43 (1H, d, J=9.3Hz), 7.75 (1H, dd, J=8.8, 2.7Hz),
8.41 (1H, d, J=2.7Hz), 9.05 (1H, d, J=8.8Hz), 11.56 (1H, s).
MS (ESI) m/z: 564 (M+H)⁺.

[Example 249]

5 N¹-(5-Chloro-2-thienyl)-N²-((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]-
amino)cyclohexyl)ethanediamide hydrochloride:



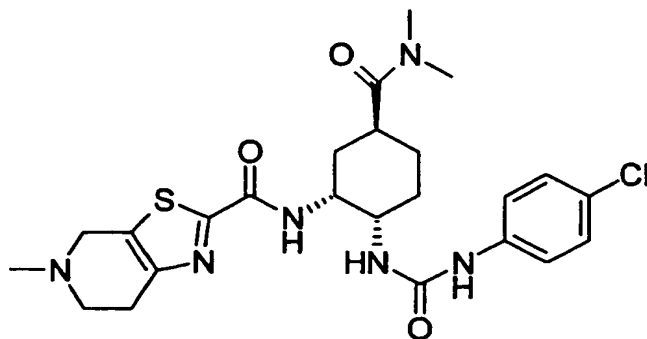
10 The title compound was obtained by hydrolyzing the
compound obtained in Referential Example 356, condensing
the hydrolyzate with the compound obtained in Referential
Example 253 and then treating the condensation product
with hydrochloric acid in a similar manner to the process
15 described in Example 191.

¹H-NMR (DMSO-d₆) δ: 1.40-1.55 (1H, m), 1.60-1.85 (3H, m),
1.90-2.15 (2H, m), 2.79 (3H, s), 2.90-3.15 (1H, m), 2.92 (3H, s),
2.94 (3H, s), 3.15-3.30 (2H, m), 3.50-3.80 (2H, m), 3.95-4.05 (1H, m),
4.35-4.90 (3H, m), 6.90 (1H, d, J=4.2Hz), 6.94 (1H, d, J=4.2Hz),
20 8.72 (1H, d, J=7.3Hz), 9.13 (1H, br. s), 11.21 (1H, br. s),
12.32 (1H, br. s).

MS (ESI) m/z : 553 (M+H)⁺.

[Example 250]

N-{(1R,2S,5S)-2-[[(4-Chloroanilino) carbonyl] amino]-5-
[(dimethylamino) carbonyl] cyclohexyl)-5-methyl-4,5,6,7-
5 tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
hydrochloride:



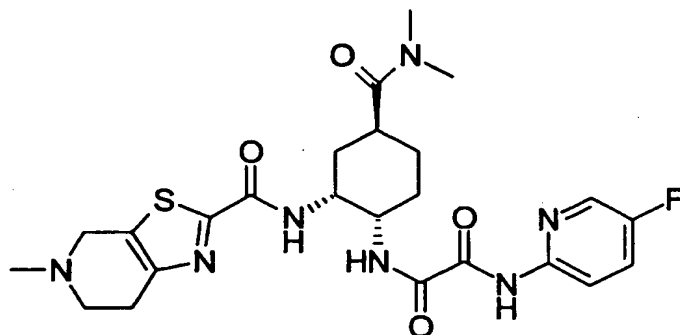
4-Chlorophenyl isocyanate (76.8 mg) was added to a
solution of the compound (183 mg) obtained in Referential
10 Example 253 in methylene chloride (20 ml), and the mixture
was stirred at room temperature for 24 hours. The solvent
was distilled off under reduced pressure, and the residue
was purified by column chromatography on silica gel
(methylene chloride:methanol = 20:1 → 10:1) to distil off
15 the solvent. The residue was dissolved in ethanol (2 ml)
and methylene chloride (2 ml), a 1N ethanol solution (0.4
ml) of hydrochloric acid was added to stir the mixture at
room temperature for 30 minutes. The reaction mixture was
concentrated under reduced pressure, and the residue was
20 solidified with diethyl ether to obtain the title compound
(160 mg).

¹H-NMR (DMSO-d₆) δ: 1.35-1.50 (1H,m), 1.60-1.90 (5H,m),
2.79 (3H,s), 2.92 (3H,s), 3.00 (3H,s), 3.10-3.60 (4H,m),
3.60-3.90 (2H,m), 4.35-4.80 (3H,m), 6.26 (1H,br.s),
7.23 (2H,d,J=9.0Hz), 7.37 (2H,d,J=9.0Hz), 8.53 (1H,br.s),
5 8.72 (1H,br.s), 11.35, 11.67 (total 1H, each s).

MS (ESI) m/z: 519 (M+H)⁺.

[Example 251]

N¹-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-[[5-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]-
10 amino)cyclohexyl)-N²-(5-fluoropyridin-2-yl)ethanediamide
hydrochloride:



The title compound was obtained by hydrolyzing the
compound obtained in Referential Example 357, condensing
15 the hydrolyzate with the compound obtained in Referential
Example 253 and then treating the condensation product
with hydrochloric acid in a similar manner to the process
described in Example 191.

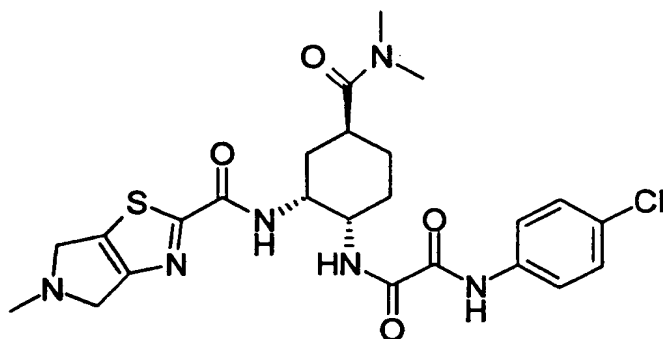
¹H-NMR (DMSO-d₆) δ: 1.47-1.53 (1H,m), 1.68-1.75 (3H,m),
20 1.99-2.10 (2H,m), 2.80 (3H,s), 2.80-3.00 (1H,m), 2.95 (6H,s),
3.18-3.21 (2H,m), 3.40-3.80 (2H,m), 3.87-4.82 (4H,m),

7.82-7.85 (1H, m), 8.01-8.05 (1H, m), 8.40 (1H, d, J=2.9 Hz),
8.71 (1H, d, J=7.7 Hz), 9.13 (1H, d, J=7.3 Hz), 10.27 (1H, s).

MS (FAB) m/z: 532 (M+H)⁺.

[Example 252]

- 5 N¹-(4-Chlorophenyl)-N²-((1S,2R,4S)-4-[(dimethylamino)-
carbonyl]-2-[[(5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]-
thiazol-2-yl) carbonyl]amino)cyclohexyl)ethanediamide
hydrochloride:



- 10 The title compound was obtained from the compound
obtained in Referential Example 242 and the compound
obtained in Referential Example 272 in a similar manner to
the process described in Example 191.

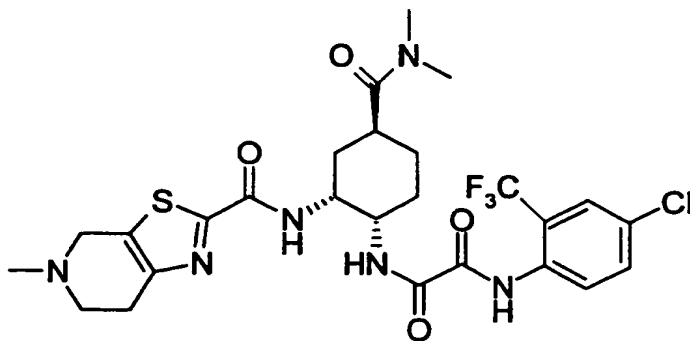
- ¹H-NMR (DMSO-d₆) δ: 1.47-1.51 (1H, m), 1.69-1.75 (3H, m),
15 1.98-2.05 (2H, m), 2.80 (3H, s), 2.95 (3H, s), 2.98-3.04 (1H, m),
3.10 (3H, s), 3.40-4.61 (6H, m), 7.41 (2H, d, J=8.8 Hz),
7.81 (2H, d, J=8.8 Hz), 8.76 (1H, d, J=7.6 Hz), 8.95 (1H, d, J=8.3 Hz),
10.79 (1H, s).

MS (FAB) m/z: 533 (M+H)⁺.

- 20 [Example 253]

N¹-[4-Chloro-2-(trifluoromethyl)phenyl]-N²-((1S,2R,4S)-4-

[(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino]-cyclohexyl)ethanediamide hydrochloride:



5 Thionyl chloride (1 ml) was added to a chloroform solution (10 ml) of the compound (269 mg) obtained in Referential Example 359, and the mixture was stirred at 75°C for 30 minutes. The solvent was distilled off under reduced pressure, and the residue was dried. To the
10 residue were added a methylene chloride solution (7 ml) of the compound (286 mg) obtained in Referential Example 253 and pyridine (3 ml) under ice cooling. The mixture was stirred for 2 hours while the temperature of the system was raised to room temperature. A saturated aqueous
15 solution (10 ml) of sodium hydrogencarbonate was added to the reaction mixture to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was subjected to
20 column chromatography on silica gel (methylene chloride:methanol = 20:1) and column chromatography on LH-

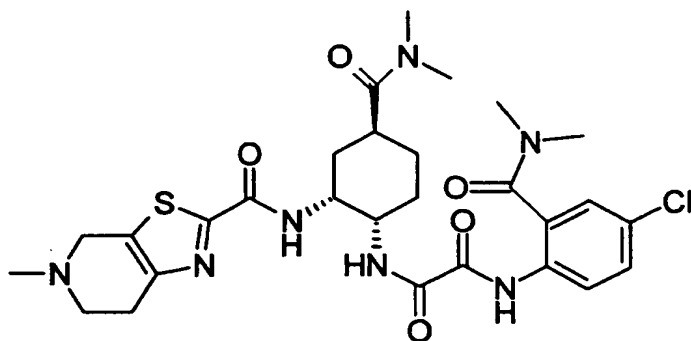
20 (molecular sieve, methanol) to obtain a free base (90 mg) of the title compound as a pale yellow amorphous solid. Methylene chloride (5 ml), ethanol (5 ml) and a 1N ethanol solution (1 ml) of hydrochloric acid were added to this product, and distilling-off and drying were conducted under reduced pressure to obtain the title compound.

¹H-NMR (DMSO-d₆) δ: 1.41-1.55 (1H, m), 1.59-1.80 (3H, m), 1.98-2.13 (2H, m), 2.77 (3H, s), 2.91 (6H, s), 3.12-3.26 (2H, m), 3.30-3.58 (2H, m), 3.60-3.78 (1H, m), 3.94-4.04 (1H, m), 4.35-4.63 (2H, m), 4.64-4.80 (1H, m), 7.73-7.82 (2H, m), 7.85 (1H, s), 8.68-8.73 (1H, m), 9.18 (1H, br. s), 10.31 (1H, s).

MS (ESI)m/z: 615 (M+H).

[Example 254]

N¹-{4-Chloro-2-[(dimethylamino)carbonyl]phenyl}-N²-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino)cyclohexyl)ethanediamide hydrochloride:



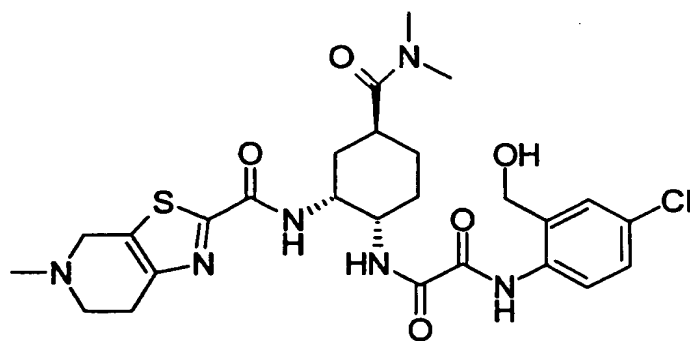
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 362, condensing the hydrolyzate with the compound obtained in Referential

Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 191.

¹H-NMR (DMSO-d₆) δ: 1.42-1.56(1H,m), 1.59-1.82(3H,m),
5 1.98-2.14(2H,m), 2.79(3H,s), 2.91(3H,s), 2.93(3H,s),
2.95(3H,s), 2.98(3H,s), 3.10-3.30(4H,m), 3.62-3.79(1H,m),
3.92-4.01(1H,m), 4.34-4.50(2H,m), 4.66-4.79(1H,m),
7.52(1H,d,J=2.4Hz), 7.55(1H,dd,J=2.4,8.5Hz),
8.05(1H,d,J=8.5Hz), 8.75(1H,br), 9.10-9.24(1H,m), 10.52(1H,s).
10 MS (ESI) m/z: 618(M+H)⁺.

[Example 255]

N¹-[4-Chloro-2-(hydroxymethyl)phenyl]-N²-((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-
15 cyclohexyl)ethanediamide hydrochloride:



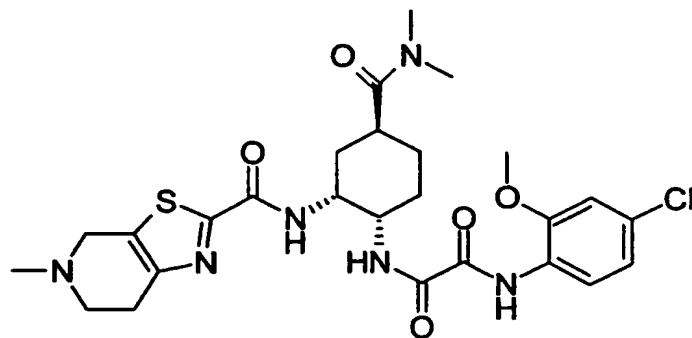
The title compound was obtained by condensing the compound obtained in Referential Example 270 with 4-chloro-2-hydroxymethylaniline and then treating the
20 condensation product with hydrochloric acid in a similar manner to the process described in Example 199.

¹H-NMR (DMSO-d₆) δ: 1.42-1.57 (1H,m), 1.58-1.81 (3H,m),
1.98-2.14 (2H,m), 2.79 (3H,s), 2.93 (6H,s), 3.12-3.58 (4H,m),
3.67-3.80 (1H,m), 3.94-4.04 (1H,m), 4.37-4.50 (1.5H,m),
4.55 (2H,s), 4.67-4.80 (1H,m), 5.77-5.92 (0.5H,m),
5 7.37 (1H,dd, J=2.4, 8.6Hz), 7.42 (1H,d, J=2.4Hz),
7.91 (1H,d, J=8.6Hz), 8.74-8.81 (1H,m), 9.03-9.19 (1H,m),
10.79 (1H,s).

MS (ESI) m/z: 577 (M+H)⁺.

[Example 256]

10 N¹-(4-Chloro-2-methoxyphenyl)-N²-((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-
cyclohexyl)ethanediamide hydrochloride:



15 The title compound was obtained by hydrolyzing the
compound obtained in Referential Example 364, condensing
the hydrolyzate with the compound obtained in Referential
Example 253 and then treating the condensation product
with hydrochloric acid in a similar manner to the process
20 described in Example 191.

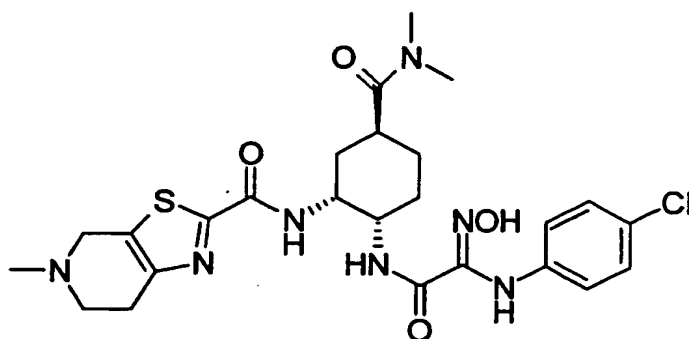
¹H-NMR (DMSO-d₆) δ: 1.40-1.55 (1H,m), 1.58-1.79 (3H,m), 1.94-

2.11 (2H, m), 2.77 (3H, s), 2.92 (6H, s), 3.05-3.55 (4H, m), 3.65-
3.75 (1H, br), 3.90 (3H, s), 3.91-4.00 (1H, m), 4.36-
4.47 (2H, br), 4.65-4.77 (1H, br), 7.04 (1H, dd, J=8.5, 2.0 Hz),
7.20 (1H, d, J=2.0 Hz), 8.06 (1H, d, J=8.5 Hz), 8.65-8.80 (1H, br),
5 9.10-9.25 (1H, br), 9.74 (1H, s), 11.10-11.35 (1H, br).

MS (ESI) m/z: 577 (M+H)⁺.

[Example 257]

N-((1R,2S,5S)-2-([2-(4-chloroanilino)-2-(
(hydroxyimino)acetyl]amino)-5-((dimethylamino)carbonyl]-
10 cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridine-2-carboxamide hydrochloride:



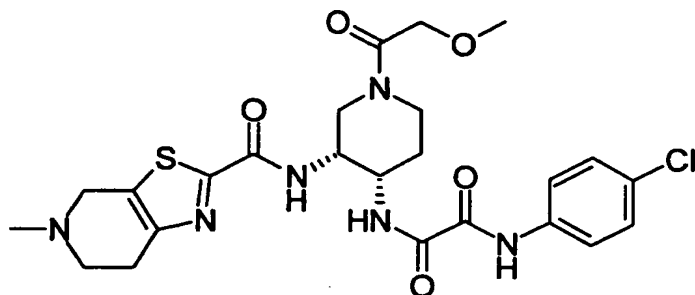
The title compound was obtained by deprotecting the
compound obtained in Referential Example 366 by
15 hydrochloric acid treatment, condensing the deprotected
compound with the compound obtained in Referential Example
10 and then treating the condensation product with
hydrochloric acid in a similar manner to the process
described in Example 214.
20 ¹H-NMR (DMSO-d₆) δ: 1.41-1.53 (1H, m), 1.57-1.77 (3H, m),
1.88-2.04 (2H, m), 2.77 (3H, s), 2.91 (6H, s), 3.00-3.60 (4H, m),

3.65-3.74 (1H, br), 3.87-3.96 (1H, m), 4.37-4.48 (2H, m),
4.66-4.76 (1H, m), 6.70 (2H, d, J=8.8 Hz),
7.04 (1H, d, J=8.8 Hz), 7.10 (1H, d, J=8.8 Hz), 8.40-8.53 (2H, m),
8.57-8.66 (1H, m), 10.30-10.47 (1H, br), 10.66-10.76 (1H, br).

5 MS (ESI) m/z: 562 (M+H)⁺.

[Example 258]

N¹-(4-Chlorophenyl)-N²-((3R,4S)-1-(2-methoxyacetyl)-3-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-carbonyl]amino}piperidin-4-yl)ethanediamide hydrochloride:



10

The title compound was obtained by deprotecting the compound obtained in Referential Example 367 by hydrochloric acid treatment, condensing the deprotected compound with the compound obtained in Referential Example 10 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 214.

¹H-NMR (DMSO-d₆) δ: 1.60-1.72 (1H, m), 1.99-2.22 (1H, m),
2.90 (3H, s), 3.03-4.80 (17H, m), 7.40 (2H, d, J=8.8 Hz),
7.83 (2H, d, J=8.8 Hz), 8.56-8.73 (1H, br), 9.14-9.33 (1H, br),
10.83 (1H, s), 11.20-11.55 (1H, br).

20

MS (ESI) m/z: 549 (M+H)⁺.

N¹-(5-Chloropyridin-2-yl)-N²-((3R,4S)-1-(2-methoxyacetyl)-3-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}piperidin-4-yl)ethanediamide

CN1CC[C@H](NC(=O)c2nc3cc[n+](c3s2)C1)c4ccccc4C(=O)NCC(=O)Nc5ccc(Cl)cn5

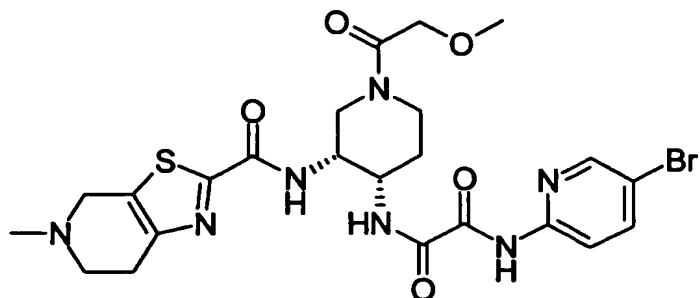
The title compound was obtained by deprotecting the compound obtained in Referential Example 368 by hydrochloric acid treatment, condensing the deprotected compound with the compound obtained in Referential Example 10 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 214.

¹H-NMR (DMSO-d₆) δ: 1.60-1.72 (1H, m), 1.98-2.20 (1H, m), 2.90 (3H, s), 3.00-4.77 (17H, m), 7.20-7.35 (0.8H, br), 7.48-7.56 (0.2H, br), 7.94-8.07 (1H, br), 8.40-8.70 (1H, br), 8.48-8.70 (1H, br), 9.23-9.45 (1H, br), 10.21-10.35 (1H, br), 11.30-11.70 (1H, br).

MS (ESI) m/z : 550 (M+H)⁺.

N¹-(5-Bromopyridin-2-yl)-N²-((3R,4S)-1-(2-methoxyacetyl)-3-
 {[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]amino}piperidin-4-yl)ethanediamide
hydrochloride:



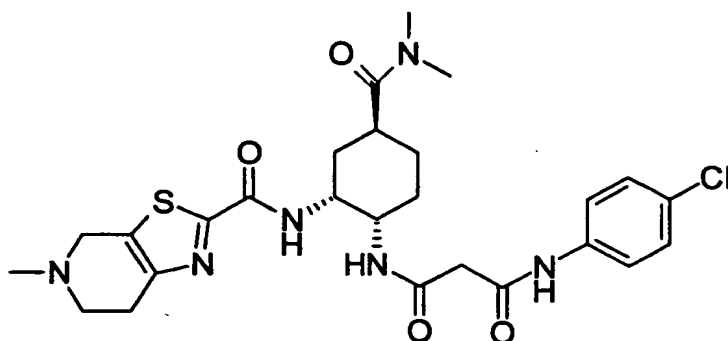
The title compound was obtained by deprotecting the
5 compound obtained in Referential Example 369 by
hydrochloric acid treatment, condensing the deprotected
compound with the compound obtained in Referential Example
10 and then treating the condensation product with
hydrochloric acid in a similar manner to the process
10 described in Example 214.

¹H-NMR (DMSO-d₆) δ: 1.60-1.73 (1H, m), 1.97-2.20 (1H, m),
2.90 (3H, s), 3.03-3.52 (7H, m), 3.64-4.07 (5H, m), 4.10-4.50 (4H, m),
4.65-4.78 (1H, m), 7.28-7.35 (0.2H, m), 7.97 (1H, d, J=8.8Hz),
8.11 (1H, dd, J=8.8, 2.2Hz), 8.51 (1H, d, J=2.2Hz), 8.55-8.67 (1H, m),
15 9.22-9.41 (1H, m), 10.20-10.31 (0.8H, m), 11.25-11.70 (1H, br).

MS (ESI) m/z: 594 (M+H)⁺.

[Example 261]

N¹-(4-Chlorophenyl)-N³-((1S,2R,4S)-4-[(dimethylamino)-
carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
20 pyridin-2-yl)carbonyl]amino}cyclohexyl)malonamide
hydrochloride:

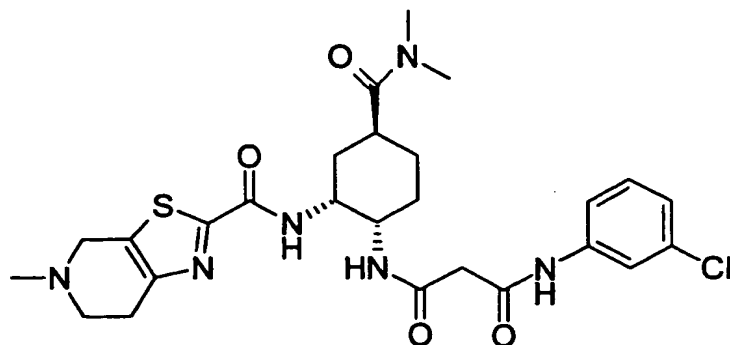


The title compound was obtained by condensing the compound obtained in Referential Example 371 with the compound obtained in Referential Example 253 and then
 5 treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 5.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.32-1.50 (1H,m), 1.55-1.87 (5H,m),
 2.78 (3H,m), 2.92 (3H,s), 2.98 (3H,s), 2.99-3.00 (1H,m),
 3.05-3.50 (5H,m), 3.65-3.75 (1H,m), 3.80-3.92 (1H,m),
 10 4.35-4.45 (1H,m), 4.45-4.55 (1H,m), 4.65-4.80 (1H,m),
 7.34 (2H,d, $J=8.8\text{Hz}$), 7.58 (2H,d, $J=8.8\text{Hz}$), 8.00-8.10 (1H,m),
 8.30-8.40 (1H,m), 10.29 (1H,d, $J=12.5\text{Hz}$), 12.40 (1H,br.s)
 MS (FAB) m/z : 561 ($\text{M}+\text{H}$) $^+$.

[Example 262]

15 N^1 -(3-Chlorophenyl)- N^3 -((1S,2R,4S)-4-((dimethylamino)-carbonyl)-2-((5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl)amino)cyclohexyl)malonamide hydrochloride:



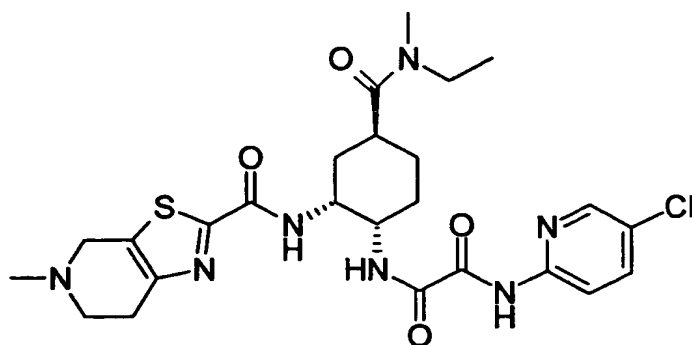
The title compound was obtained by condensing the compound obtained in Referential Example 373 with the compound obtained in Referential Example 253 and then
 5 treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 5.

¹H-NMR (DMSO-d₆) δ: 1.32-1.50 (1H, m), 1.55-1.90 (5H, m),
 2.77 (3H, s), 2.91 (3H, s), 2.98 (3H, s), 2.99-3.00 (1H, m),
 3.05-3.50 (5H, m), 3.65-3.80 (1H, m), 3.80-3.90 (1H, m),
 4.35-4.50 (1H, m), 4.50-4.60 (1H, m), 4.65-4.80 (1H, m),
 7.09 (1H, d, J=8.8Hz), 7.31 (1H, d, J=8.8Hz), 7.38 (1H, t, J=8.8Hz),
 7.79 (1H, s), 8.00-8.10 (1H, m), 8.30-8.40 (1H, m),
 10.28 (1H, d, J=12.5Hz), 11.67 (1H, br. s).

MS (FAB) m/z: 561 (M+H)⁺.

15 [Example 263]

N¹-(5-Chloropyridin-2-yl)-N²-((1S,2R,4S)-4-
 {[ethyl(methyl)amino]carbonyl}-2-[(5-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
 amino)cyclohexyl)ethanediamide hydrochloride:



10% Palladium on carbon (0.3 g) was added to a solution of the compound (0.33 g) obtained in Referential Example 404 in ethanol (20 ml), and the mixture was

5 stirred at room temperature for 24 hours under a hydrogen atmosphere. After removing insoluble matter by filtration through Celite pad, the filtrate was concentrated under reduced pressure. The resultant residue (0.37 g) was dissolved in N,N-dimethylformamide (20 ml), and the

10 compound (0.3 g) obtained in Referential Example 266, 1-hydroxybenzotriazole monohydrate (0.2 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.37 g) were successively added to stir the mixture at room temperature for 18 hours. The reaction mixture was

15 concentrated under reduced pressure, and the resultant residue was diluted with a mixed solvent of chloroform-methanol (9:1) and washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. After the resultant organic

20 layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure, the

resultant residue was purified by column chromatography on silica gel (chloroform:methanol = 95:5) to concentrate the intended fraction. A 1N ethanol solution of hydrochloric acid was added to form a hydrochloride. This salt was

5 recrystallized from a mixed solvent of methanol and diethyl ether to obtain the title compound (0.28 g).

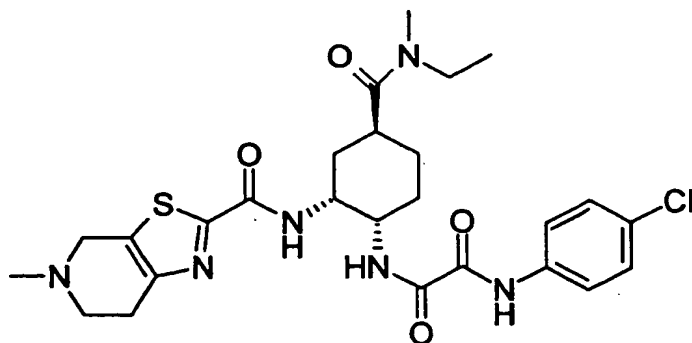
$^1\text{H-NMR}$ (DMSO-d_6) δ : 0.95 (1.5H, t, $J=6.9\text{Hz}$),
1.42 (1.5H, t, $J=6.9\text{Hz}$), 1.40-1.52 (1H, m), 1.60-1.78 (3H, m),
1.92-2.11 (2H, m), 2.74 (3H, s), 2.90 (3H, s), 3.10-3.38 (5H, m),
10 3.40-3.52 (1H, m), 3.68-3.70 (1H, m), 3.96-4.05 (1H, m), 4.41 (2H, s),
4.70 (1H, d, $J=15.9\text{Hz}$), 8.00-8.01 (2H, m), 8.44 (1H, s),
8.71 (1H, dd, $J=10.1, 2.2\text{Hz}$), 9.14 (0.5H, d, $J=7.8\text{Hz}$),
9.22 (0.5H, d, $J=8.3\text{Hz}$), 10.24 (0.5H, s), 10.28 (0.5H, s),
11.48 (1H, br. s), 11.61 (1H, br. s).

15 MS (FAB) m/z : 562 ($\text{M}+\text{H}$) $^+$.

[Example 264]

N^1 -(4-Chlorophenyl)- N^2 -((1S,2R,4S)-4-{[ethyl(methyl)amino]-carbonyl}-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide

20 hydrochloride:

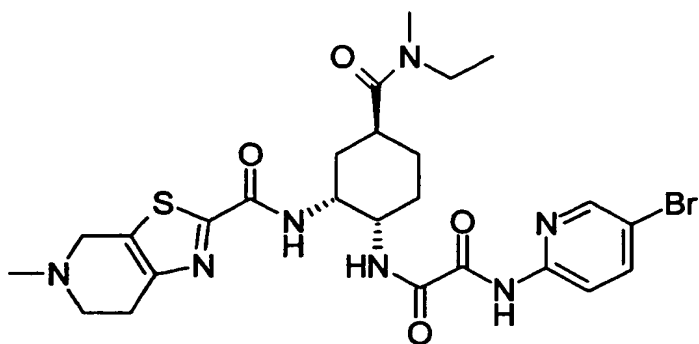


The title compound was obtained by converting the compound obtained in Referential Example 404 into an amine, condensing the amine with the compound obtained in Referential Example 374 and then treating the condensation
5 product with hydrochloric acid in a similar manner to the process described in Example 263.

¹H-NMR (DMSO-d₆) δ: 0.97 (1.5H, t, J=6.9Hz),
1.04 (1.5H, t, J=6.9Hz), 1.40-1.60 (1H, m), 1.60-1.80 (3H, m),
1.92-2.11 (2H, m), 2.74 (3H, s), 2.89 (3H, s), 3.10-3.32 (5H, m),
10 3.40-3.52 (1H, m), 3.65-3.80 (1H, m), 3.90-4.05 (1H, m),
4.40 (2H, s), 4.70 (1H, d, J=15.9Hz), 7.39 (2H, d, J=8.8Hz),
7.82 (2H, d, J=8.8Hz), 8.75 (1H, dd, J=10.1, 2.2Hz),
9.00 (0.5H, d, J=7.8Hz), 9.08 (0.5H, d, J=8.3Hz),
10.81 (1H, d, J=4.9Hz), 11.45 (1H, br. s).
15 MS (FAB) m/z: 561 (M+H)⁺.

[Example 265]

N¹-(5-Bromopyridin-2-yl)-N²-((1S,2R,4S)-4-
{[ethyl(methyl)amino]carbonyl}-2-{{(5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
20 amino}cyclohexyl)ethanediamide hydrochloride:



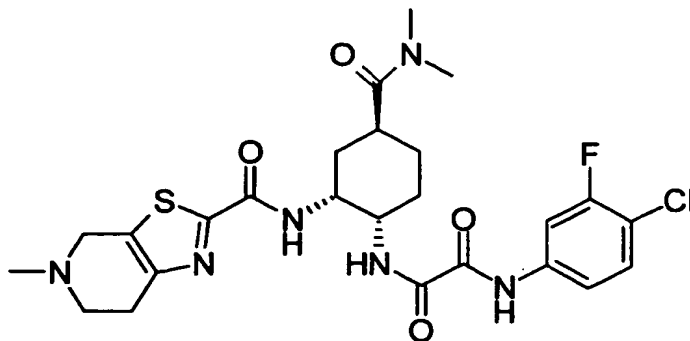
The title compound was obtained by converting the compound obtained in Referential Example 404 into an amine, condensing the amine with the compound obtained in Referential Example 375 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 263.

¹H-NMR (DMSO-d₆) δ: 1.02 (1.5H, t, J=6.9Hz), 1.08 (1.5H, t, J=6.9Hz), 1.49-1.60 (1H, m), 1.60-1.86 (3H, m), 2.00-2.20 (2H, m), 2.81 (3H, s), 2.97 (3H, s), 3.15-3.42 (6H, m), 3.50-3.60 (1H, m), 3.70-3.82 (1H, m), 4.48 (2H, s), 4.77 (1H, d, J=15.9Hz), 8.04 (1H, d, J=8.8Hz), 8.17 (1H, d, J=8.8Hz), 8.58 (1H, s), 8.78 (1H, dd, J=10.1, 2.2Hz), 9.21 (0.5H, d, J=7.8Hz), 9.29 (0.5H, d, J=8.3Hz), 10.29 (0.5H, s), 10.33 (0.5H, s), 11.53 (0.5H, br. s), 11.65 (0.5H, br. s).

MS (FAB) m/z: 607 (M+H)⁺.

[Example 266]

N¹-(4-Chloro-3-fluorophenyl)-N²-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino)cyclohexyl)ethanediamide hydrochloride:



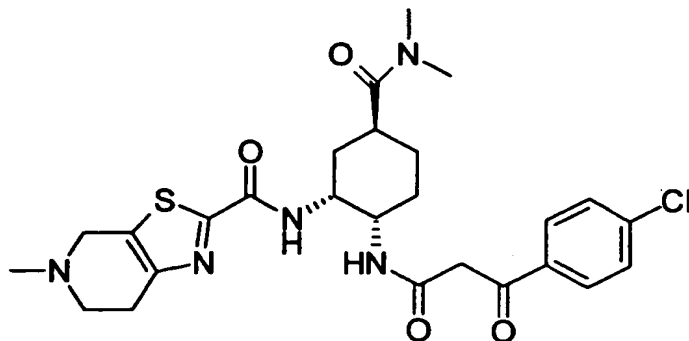
The title compound was obtained by converting the compound obtained in Referential Example 252 into an amine, condensing the amine with the compound obtained in Referential Example 378 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 263.

¹H-NMR (DMSO-d₆) δ: 1.44-1.52 (1H,m), 1.65-1.76 (3H,m), 2.01-2.07 (2H,m), 2.77 (3H,s), 2.93 (6H,s), 2.94-3.00 (1H,m), 3.10-3.38 (3H,m), 3.68-3.70 (1H,m), 3.96-4.05 (1H,m), 4.42 (2H,s), 4.70 (1H,d,J=15.9Hz), 7.56 (1H,t,J=8.8Hz), 7.68 (1H,d,J=8.8Hz), 7.90 (1H,dd,J=11.7,1.5Hz), 8.73 (1H,dd,J=12.5,7.3Hz), 9.06 (1H,dd,J=12.5,8.1Hz), 11.01 (1H,d,J=5.8Hz), 11.30-11.42 (1H,m).

MS (FAB) m/z: 565 (M+H)⁺.

[Example 267]

N-{(1R,2S,5S)-2-{[3-(4-Chlorophenyl)-3-oxopropanoyl]amino}-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:



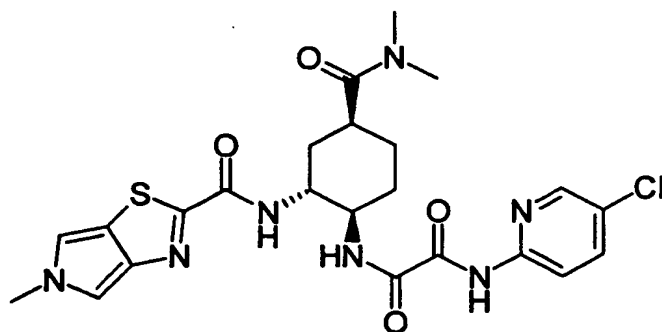
The title compound was obtained by deprotecting the

compound obtained in Referential Example 383 by
hydrochloric acid treatment, condensing the deprotected
compound with the compound obtained in Referential Example
10 and then treating the condensation product with
5 hydrochloric acid in a similar manner to the process
described in Example 214.

$^1\text{H-NMR}$ (CDCl_3) (free base) δ : 1.22-1.32 (1H,m), 1.49-
1.92 (3H,m), 1.95-2.10 (2H,m), 2.53 (3H,s), 2.70-2.79 (1H,m),
2.80-2.90 (2H,m), 2.93 (6H,s), 2.95-3.09 (2H,m), 3.72 (2H,s),
10 3.87 (2H,s), 4.05-4.19 (1H,m), 4.60-4.70 (1H,m), 7.20-
7.40 (2H,m), 7.42 (2H,d, $J=8.3\text{Hz}$), 7.87 (2H,d, $J=8.3\text{Hz}$).
MS (FAB) m/z : 546 ($\text{M}+\text{H}$) $^+$.

[Example 268]

N^1 -(5-Chloropyridin-2-yl)- N^2 -((1R,2R,4S)-4-
15 [(dimethylamino)carbonyl]-2-[[(5-methyl-5H-pyrrolo[3,4-d]-
thiazol-2-yl)carbonyl]amino}cyclohexyl)ethanediamide:



The title compound was obtained by deprotecting the
compound obtained in Referential Example 386 by
20 hydrochloric acid treatment, and condensing the
deprotected compound with the compound obtained in

Referential Example 293 in a similar manner to the process described in Example 214.

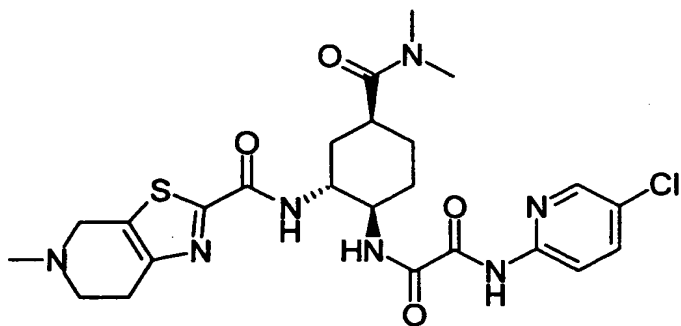
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.00-2.35 (7H, m), 2.96 (3H, s), 3.04 (3H, s),
3.85-3.95 (1H, m), 3.88 (3H, s), 4.60-4.75 (1H, m),
5 6.68 (1H, d, $J=2.0\text{Hz}$), 7.17 (1H, d, $J=2.0\text{Hz}$), 7.20-7.32 (1H, m),
7.67 (1H, dd, $J=8.8, 2.8\text{Hz}$), 7.99 (1H, d, $J=8.4\text{Hz}$),
8.21 (1H, d, $J=8.8\text{Hz}$), 8.25 (1H, d, $J=2.8\text{Hz}$), 9.64 (1H, s).

HRMS (FAB) m/z : 532.1520 ($\text{M}+\text{H}$) $^+$.

(Calculated; $\text{C}_{23}\text{H}_{27}\text{ClN}_7\text{O}_4\text{S}$: 532.1534).

10 [Example 269]

N^1 -[(5-Chloropyridin-2-yl)amino]- N^2 -((1R,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
amino)cyclohexyl)ethanediamide hydrochloride:



15

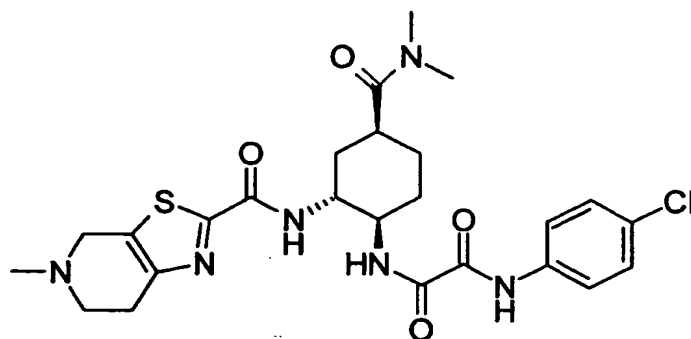
The title compound was obtained by reducing the compound obtained in Referential Example 387 in a similar manner to the process described in Referential Example 253, and condensing the reduction product with the compound
20 obtained in Referential Example 266 and treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 208.

¹H-NMR (DMSO-d₆) δ: 1.50-1.98 (6H, m), 2.82 (3H, s), 2.91 (3H, s), 2.95 (3H, s), 2.86-3.92 (7H, m), 4.30-4.81 (2H, m), 7.92-8.09 (2H, m), 8.39-8.47 (1H, m), 8.56-8.72 (2H, m), 10.17 (1H, s).

MS (ESI) m/z: 548 (M+H)⁺.

5 [Example 270]

N¹-(4-Chlorophenyl)-N²-((1R,2R,4S)-4-[(dimethylamino)-carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide:



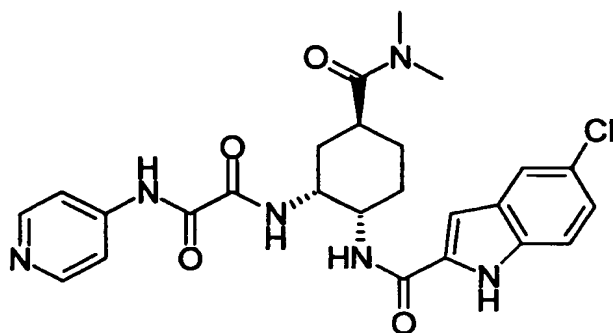
10 The title compound was obtained by reducing the compound obtained in Referential Example 387 in a similar manner to the process described in Referential Example 253, and condensing the reduction product with the lithium salt
15 Referential Example 242 and treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 191.

¹H-NMR (DMSO-d₆) δ: 1.50-1.97 (6H, m), 2.82 (3H, s), 2.91 (3H, s), 2.98 (3H, s), 2.83-3.88 (7H, m), 4.30-4.79 (2H, m),
20 7.37 (2H, d, J=8.8Hz), 7.89 (2H, d, J=8.8Hz), 8.34 (1H, d, J=8.4Hz), 8.63 (1H, d, J=8.8Hz), 10.72 (1H, s).

MS (ESI) m/z : 547 ($M+H$)⁺.

[Example 271]

N¹-{(1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-
[(dimethylamino)carbonyl]cyclohexyl}-N²-(pyridin-4-yl)-
5 ethanediamide hydrochloride:



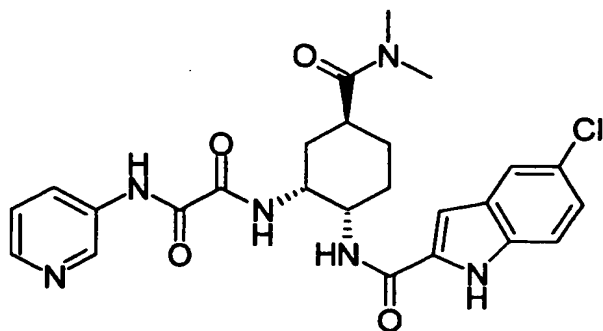
The title compound was obtained by deprotecting the
compound obtained in Referential Example 310 by
hydrochloric acid treatment, and condensing the
10 deprotected compound with lithium 2-[(pyridin-4-yl)amino]-
2-oxoacetate obtained by hydrolyzing the compound obtained
in Referential Example 261 and then treating the
condensation product with hydrochloric acid in a similar
manner to the process described in Example 191.

15 ¹H-NMR (DMSO-d₆) δ: 1.40-2.01(6H,m), 2.79(3H,s), 3.01(3H,s),
3.00-3.18(1H,m), 4.02-4.19(1H,m), 4.45-4.55(1H,m), 7.09(1H,s),
7.13-7.22(1H,m), 7.41(1H,d,J=8.4Hz), 7.64(1H,br.s),
8.28(2H,d,J=6.8Hz), 8.36(1H,d,J=8.0Hz), 8.62(1H,d,J=8.8Hz),
8.72(2H,d,J=6.8Hz), 11.74(1H,s), 11.83(1H,s).

20 MS (FAB) m/z : 511 ($M+H$)⁺.

[Example 272]

N¹-{(1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl}-N²-(pyridin-3-yl)-ethanediamide hydrochloride:



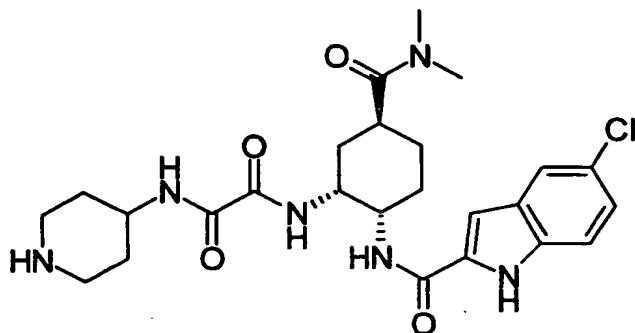
5 The title compound was obtained by using methyl 2-[(pyridin-3-yl)amino]-2-oxoacetate obtained by condensing 3-aminopyridine with methyl 2-chloro-2-oxoacetate in a similar manner to the process described in Referential Example 242, and the compound obtained in Referential
10 Example 310 as raw materials in a similar manner to the process described in Example 271.

¹H-NMR (DMSO-d₆) δ: 1.40-2.05 (6H, m), 2.80 (3H, s), 3.02 (3H, s), 2.92-3.15 (1H, m), 4.02-4.17 (1H, m), 4.42-4.58 (1H, m), 7.10 (1H, s), 7.12-7.19 (1H, m), 7.40 (1H, d, J=8.4 Hz), 7.62-7.87 (2H, m),
15 8.36-8.64 (4H, m), 9.18 (1H, s), 11.39 (1H, s), 11.79 (1H, s).

MS (FAB) m/z: 511 (M+H)⁺.

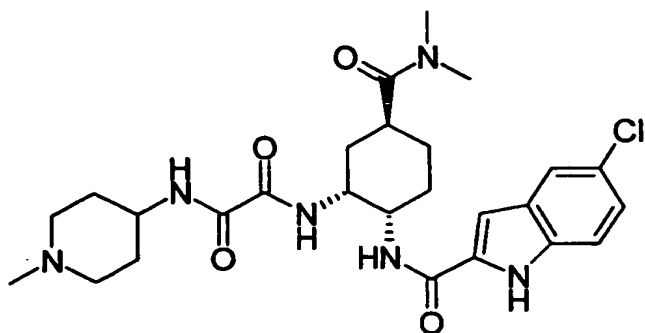
[Example 273]

N¹-{(1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl}-N²-(piperidin-4-yl)-
20 ethanediamide hydrochloride:



- A 4N dioxane solution (8.0 ml) of hydrochloric acid was added to a solution of the compound (400 mg) obtained in Referential Example 389 in ethanol (5.0 ml) at room temperature and the mixture was stirred the same temperature for 5 hours. The solvent was distilled off under reduced pressure, the residue was washed with methylene chloride, and insoluble matter was filtered and washed to obtain the title compound (320 mg).
- ¹H-NMR (DMSO-d₆) δ: 1.38-1.92(10H,m), 2.77(3H,s), 2.96(3H,s), 2.82-3.35(6H,m), 3.88-4.10(2H,m), 4.34-4.43(1H,m), 7.05(1H,s), 7.11-7.17(1H,m), 7.38(1H,d,J=8.8Hz), 7.65(1H,s), 8.25(1H,d,J=8.0Hz), 8.34(1H,d,J=7.6Hz), 8.89(1H,d,J=8.4Hz), 11.75(1H,s).
- MS (ESI) m/z: 517(M+H)⁺.
- [Example 274]

N¹-{(1R,2S,5S)-2-[[(5-Chloroindol-2-yl)carbonyl]amino]-5-[(dimethylamino)carbonyl]cyclohexyl}-N²-(1-methylpiperidin-4-yl)ethanediamide hydrochloride:



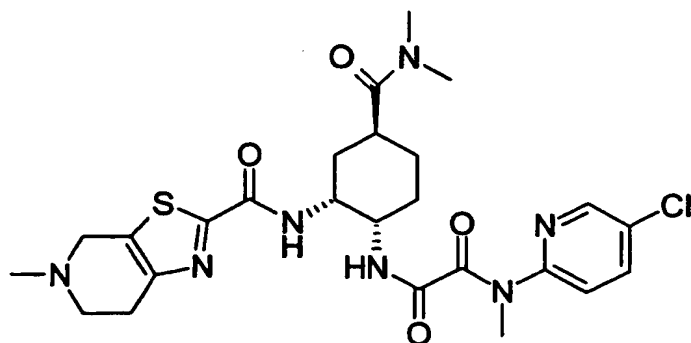
The title compound was obtained by methylating the compound obtained in Example 273 in a similar manner to the process described in Referential Example 9 and
 5 treating it with hydrochloric acid.

¹H-NMR (DMSO-d₆) δ: 1.40-2.01 (11H, m), 2.67 (3H, s), 2.79 (3H, s),
 2.98 (3H, s), 2.85-4.48 (7H, m), 7.07 (1H, s),
 7.16 (1H, dd, J=8.8, 2.0 Hz), 7.40 (1H, d, J=8.8 Hz),
 7.68 (1H, d, J=2.0 Hz), 8.25-8.35 (1H, m), 8.37 (1H, d, J=7.6 Hz),
 10 8.90-9.02 (1H, m), 9.82 (1H, br. s), 11.78 (1H, s).

MS (ESI) m/z: 531 (M+H)⁺.

[Example 275]

N¹-(5-Chloropyridin-2-yl)-N²-((1S,2R,4S)-4-
 [(dimethylamino)carbonyl]-2-[(5-methyl-4,5,6,7-
 15 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
 amino)cyclohexyl)-N¹-methylethanedi- amide hydrochloride:



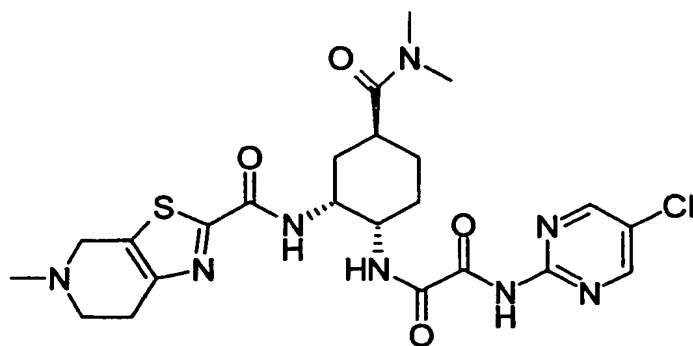
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 390, condensing the hydrolyzate with the compound obtained in Referential
 5 Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 191.

¹H-NMR (DMSO-d₆) δ: 1.32-1.97(6H,m), 2.42-2.51(1H,m),
 2.76(3H,s), 2.91(3H,s), 2.93(3H,s), 3.27(3H,s),
 10 3.00-4.80(8H,m), 7.45(1H,br.s), 7.88-7.97(1H,m),
 8.25-8.41(2H,m), 8.78-8.91(1H,m).

MS (FAB) m/z: 562(M+H)⁺.

[Example 276]

N¹-(5-Chloropyrimidin-2-yl)-N²-((1S,2R,4S)-4-
 15 [(dimethylamino)carbonyl]-2-[(5-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
 amino)cyclohexyl)ethanediamide hydrochloride:



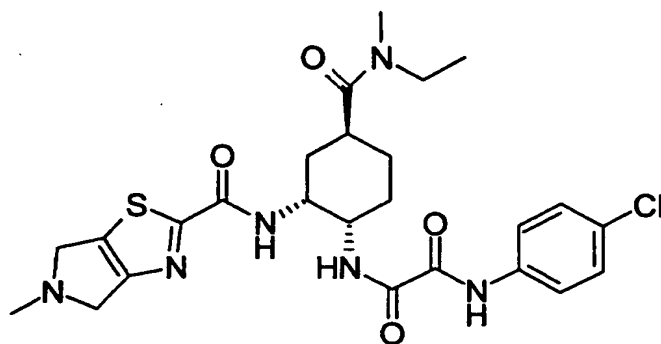
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 391, condensing the hydrolyzate with the compound obtained in Referential Example 253 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 191.

¹H-NMR (DMSO-d₆) δ: 1.38-2.10 (7H, m), 2.77 (3H, s), 2.90 (3H, s), 2.93 (3H, s), 3.04-4.80 (8H, m), 8.60-8.70 (2H, m), 8.82 (2H, s), 9.08 (1H, br. s), 10.64 (1H, s), 11.57 (1H, br. s).

MS (FAB) m/z: 549 (M+H)⁺.

[Example 277]

N¹-(4-Chlorophenyl)-N²-((1S,2R,4S)-4-{{[ethyl(methyl)amino]-carbonyl}-2-{{[(5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]-thiazol-2-yl)carbonyl]amino}cyclohexyl)ethanediamide hydrochloride:



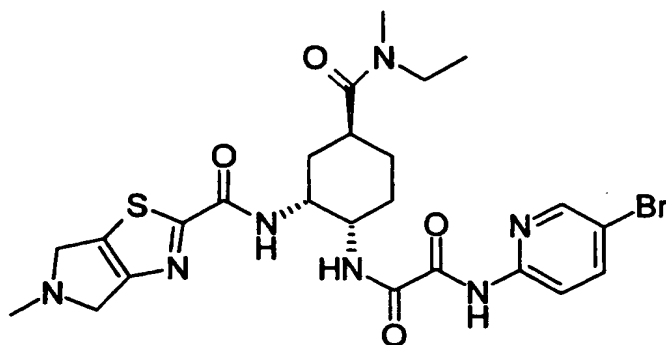
The title compound was obtained by reducing the compound obtained in Referential Example 392 in a similar manner to the process described in Referential Example 253, and condensing the reduction product with the carboxylic acid obtained by hydrolyzing the compound obtained in Referential Example 242 and treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 195.

¹H-NMR (DMSO-d₆) δ: 0.96, 1.02 (3H, each t, J=7.0Hz), 1.47-1.58 (1H, m), 1.65-1.77 (3H, m), 1.98-2.08 (2H, m), 2.76-2.91 (4H, m), 3.07 (3H, s), 3.19-3.41 (2H, m), 3.98-4.04 (1H, m), 4.42 (1H, br. s), 4.46-4.94 (4H, m), 7.41 (2H, d, J=8.8Hz), 7.83 (2H, d, J=8.8Hz), 8.74-8.80 (1H, m), 9.02 (1H, d, J=7.3Hz), 10.82 (1H, s), 12.41 (1H, br. s).

MS (FAB) m/z: 547 (M+H)⁺.

[Example 278]

N¹-(5-Bromopyridin-2-yl)-N²-((1S,2R,4S)-4-([ethyl(methyl)amino]carbonyl)-2-({[(5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)carbonyl]amino}cyclohexyl)-ethanediamide hydrochloride:



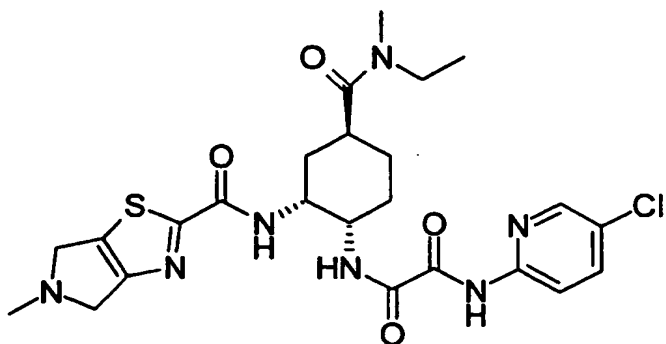
The title compound was obtained from the compound obtained in Referential Example 392 and the compound obtained in Referential Example 262 in a similar manner to
 5 the process described in Example 277.

¹H-NMR (DMSO-d₆) δ: 0.90-1.08 (3H,m), 1.40-2.13 (6H,m),
 2.70-3.53 (13H,m), 3.92-4.08 (1H,m), 4.35-4.47 (1H,m),
 7.95 (1H,d,J=8.8Hz), 8.10 (1H,dd,J=8.8,2.4Hz), 8.50-8.55 (1H,m),
 8.68-8.78 (1H,m), 9.12-9.18 (1H,m), 10.26 (1H,s).

10 MS (FAB) m/z: 592 (M+H)⁺.

[Example 279]

N¹-(5-Chloropyridin-2-yl)-N²-((1S,2R,4S)-4-
 {[ethyl(methyl)amino]carbonyl}-2-{{[(5-methyl-5,6-dihydro-
 4H-pyrrolo[3,4-d]thiazol-2-yl)carbonyl]amino}cyclohexyl)-
 15 ethanediamide hydrochloride:



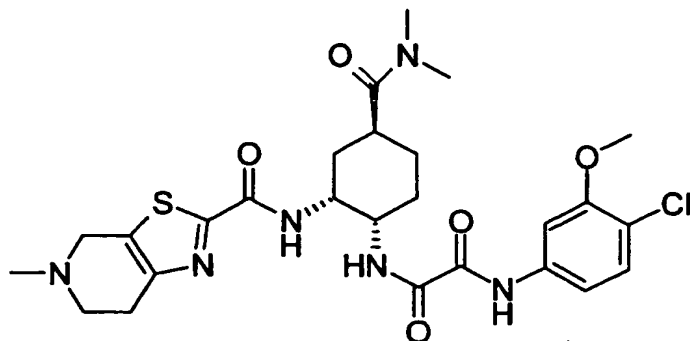
The title compound was obtained from the compound obtained in Referential Example 392 and the compound obtained in Referential Example 243 in a similar manner to the process described in Example 277.

¹H-NMR (DMSO-d₆) δ: [0.95 (t, J=7.0Hz), 1.01 (t, J=6.8Hz), 3H], 1.45-1.72 (4H, m), 1.96-2.07 (2H, m), 2.74-2.90 (4H, m), 3.06 (3H, s), 3.18-3.40 (2H, m), 3.95-4.02 (1H, m), 4.41 (1H, br. s), 4.54-4.90 (4H, m), 8.00 (2H, br. s), 8.45 (1H, s), 8.70-8.75 (1H, m), 9.15 (1H, br. s), 10.27 (1H, br. s), 12.29 (1H, br. s).

MS (ESI) m/z: 548 (M+H)⁺.

[Example 280]

N¹-(4-Chloro-3-methoxyphenyl)-N²-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino)cyclohexyl)ethanediamide hydrochloride:



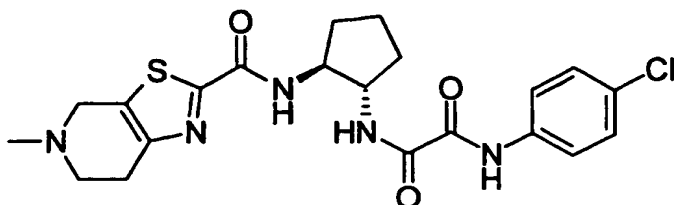
The title compound was obtained by condensing the compound obtained in Referential Example 395 with the compound obtained in Referential Example 10 and treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 2.

¹H-NMR (DMSO-d₆) δ: 1.46-1.54 (1H, m), 1.67-1.77 (3H, m), 2.01-2.10 (2H, m), 2.79 (3H, s), 2.92-2.98 (7H, m), 3.21 (2H, br. s), 3.49 (1H, br. s), 3.69 (1H, br. s), 3.80 (3H, s), 3.98-4.03 (1H, m), 4.42-4.50 (2H, m), 4.69 (1H, br. s), 7.37 (1H, d, J=8.7 Hz), 7.48 (1H, dd, J=8.7, 2.2 Hz), 7.72 (1H, d, J=2.2 Hz), 8.75 (1H, d, J=7.3 Hz), 9.06 (1H, br. s), 10.77 (1H, s), 11.44 (1H, br. s).

MS (FAB) m/z: 577 (M+H)⁺.

[Example 281]

N¹-(4-Chlorophenyl)-N²-((1R*,2R*)-2-({[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino}cyclopentyl)ethanediamide hydrochloride:



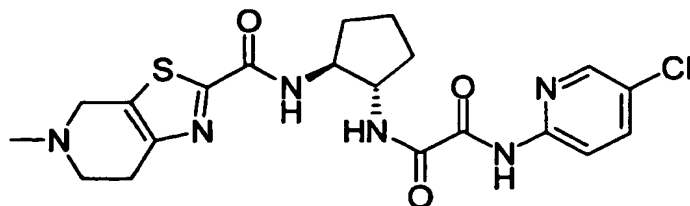
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 242, condensing the hydrolyzate with the compound obtained in Referential Example 62 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 195.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.65-1.73(4H,m), 1.91-1.96(2H,m), 2.91(3H,s), 3.15(2H,br.s), 3.49(1H,br.s), 3.66(1H,br.s), 4.32-4.42(3H,m), 4.66(1H,br.s), 7.40(2H,d,J=8.9Hz), 7.84(2H,d,J=8.9Hz), 8.92(1H,d,J=8.5Hz), 9.03(1H,d,J=8.3Hz), 10.76(1H,s), 11.32(1H,br.s).

MS (FAB) m/z : 462($\text{M}+\text{H}$) $^+$.

[Example 282]

N^1 -(5-Chloropyridin-2-yl)- N^2 -((1R*,2R*)-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino)cyclopentyl)ethanediamide hydrochloride:



The title compound was obtained by condensing the compound obtained in Referential Example 62 with the

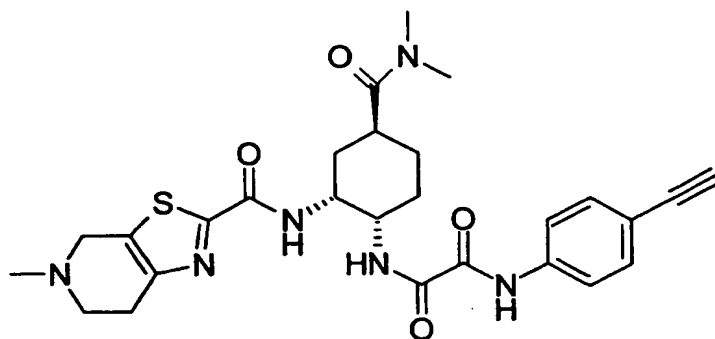
compound obtained in Referential Example 266 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 208.

5 ¹H-NMR (DMSO-d₆) δ: 1.71(4H,br.s),1.96(2H,br.s),2.90(3H,s),
3.14(1H,br.s),3.21(1H,br.s),3.47(1H,br.s),3.68(1H,br.s),
4.34-4.45(3H,m),4.66(1H,br.s),7.99-8.06(2H,m),8.43-
8.44(1H,m), 8.94(1H,d,J=8.3Hz),9.20(1H,d,J=8.5Hz),
10.20(1H,br.s), 11.78(1.1H,br.s).

10 MS (FAB) m/z: 463(M+H)⁺.

[Example 283]

N¹-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino)cyclohexyl)-N²-(4-ethynylphenyl)ethanediamide:



15

The title compound was obtained by condensing the compound obtained in Referential Example 252 with the compound obtained in Referential Example 397 in a similar manner to the process described in Example 263.

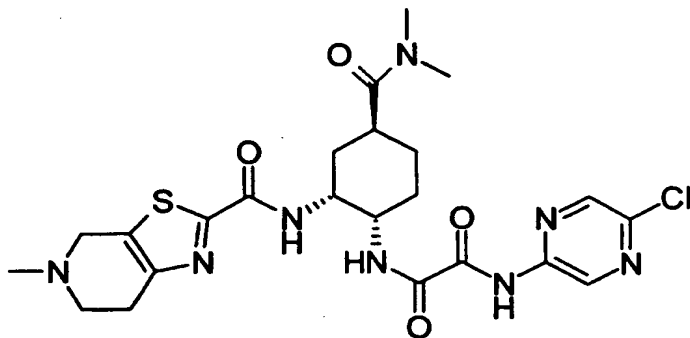
20 ¹H-NMR (CDCl₃) δ: 1.67-2.16(6H,m),2.51(3H,s),2.76-
2.91(5H,m),

2.94 (3H, s), 3.04 (3H, s), 3.07 (1H, s), [3.65 (1H, d, J=15.5Hz),
3.73 (1H, d, J=15.5Hz) AB pattern], 4.09-4.16 (1H, m), 4.72-
4.75 (1H, m), 7.42-7.46 (3H, m), 7.58 (2H, d, J=8.5Hz),
8.02 (1H, d, J=8.1Hz), 9.36 (1H, s).

5 MS (FAB) m/z: 537 (M+H)⁺.

[Example 284]

N¹-(5-Chloropyrazin-2-yl)-N²-((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
10 amino)cyclohexyl)ethanediamide hydrochloride:



The title compound was obtained by condensing the
compound obtained in Referential Example 253 with the
compound obtained in Referential Example 399 in a similar
15 manner to the process described in Referential Example 97
and then treating the condensation product with
hydrochloric acid.

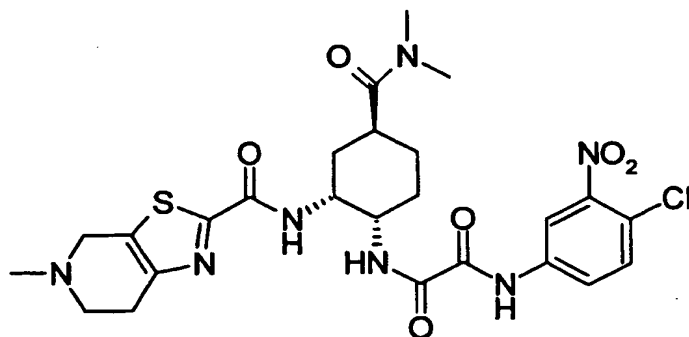
¹H-NMR (DMSO-d₆) δ: 1.44-1.52 (1H, m), 1.65-1.77 (3H, m),
2.00-2.10 (2H, m), 2.77 (3H, s), 2.91-2.97 (7H, m), 3.20 (2H, br. s),
20 3.48 (1H, br. s), 3.68 (1H, br. s), 3.97-4.02 (1H, m), 4.40-
4.46 (2H, m),

4.68 (1H, br. s), 8.64 (1H, d, J=1.2 Hz), 8.70 (1H, d, J=7.3 Hz),
9.02 (1H, s), 9.21 (1H, br. s), 10.91 (1H, br. s), 11.50 (1H, br. s).

MS (FAB) m/z: 549 (M+H)⁺.

[Example 285]

5 N¹-(4-Chloro-3-nitrophenyl)-N²-((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[5-methyl-4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
amino)cyclohexyl)ethanediamide hydrochloride:



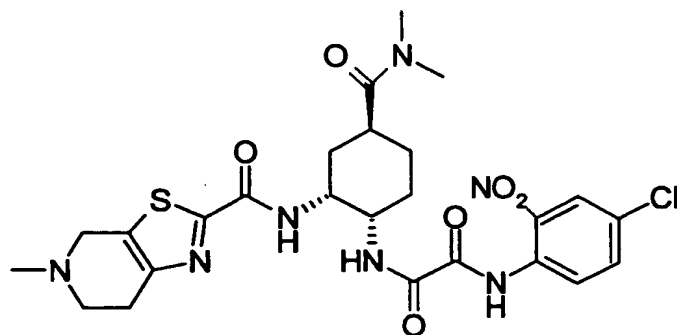
10 The title compound was obtained by condensing the
compound obtained in Referential Example 253 with the
compound obtained in Referential Example 400 in a similar
manner to the process described in Referential Example 97
and then treating the condensation product with
15 hydrochloric acid.

¹H-NMR (DMSO-d₆) δ: 1.44-1.53 (1H, m), 1.66-1.73 (3H, m),
1.97-2.07 (2H, m), 2.77 (3H, s), 2.89-3.05 (7H, m), 3.20 (2H, br. s),
3.55 (2H, br. s), 4.00 (1H, br. s), 4.44 (1H, br. s), 4.52 (2H, br. s),
7.75 (1H, d, J=8.8 Hz), 8.08 (1H, d, J=8.8 Hz), 8.59 (1H, s),
20 8.71 (1H, d, J=7.3 Hz), 9.07 (1H, d, J=8.0 Hz), 11.24 (1H, s),
11.58 (1H, br. s).

MS (FAB) m/z: 592 (M+H)⁺.

[Example 286]

N¹-(4-Chloro-2-nitrophenyl)-N²-((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-
5 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
amino)cyclohexyl)ethanediamide hydrochloride:



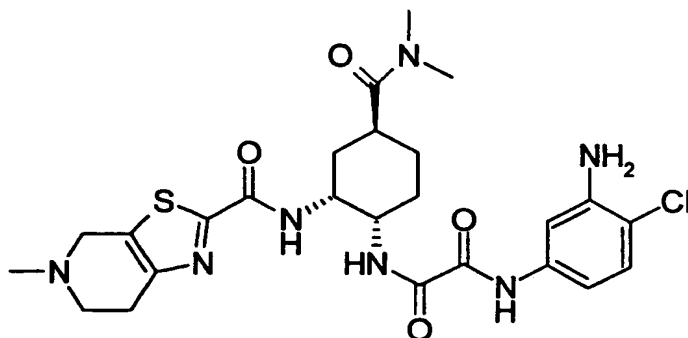
The title compound was obtained by condensing the
compound obtained in Referential Example 253 with the
10 compound obtained in Referential Example 401 and then
treating the condensation product with hydrochloric acid
in a similar manner to the process described in Example
208.

¹H-NMR (DMSO-d₆) δ: 1.46-1.54 (1H,m), 1.66-1.77 (3H,m),
15 2.03-2.10 (2H,m), 2.79 (3H,s), 2.90-2.93 (7H,m), 3.17-3.28 (2H,m),
3.49 (1H,br.s), 3.68 (1H,br.s), 3.99-4.04 (1H,m), 4.41 (1H,br.s),
4.46 (1H,br.s), 4.68 (1H,br.s), 7.89 (1H,d,J=9.0Hz), 8.20-
8.21 (2H,m), 8.73 (1H,d,J=6.4Hz), 9.28 (1H,br.s),
11.49 (1H,br.s), 11.56 (1H,s).

20 MS (FAB) m/z: 592 (M+H)⁺.

[Example 287]

N¹-(3-Amino-4-chlorophenyl)-N²-((1S,2R,4S)-4-
 [(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
 amino)cyclohexyl)ethanediamide hydrochloride:



5

The compound (236 mg) obtained in Example 285 was dissolved in ethanol (25 ml), and a catalytic amount of Raney nickel was added to stir the mixture at room temperature for 17 hours under a hydrogen atmosphere.

10 Thereafter, a catalytic amount of Raney nickel was additionally added to stir the mixture for additional 7 hours. The catalyst was removed by filtration, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica

15 gel (methylene chloride:methanol = 23:2) to obtain a pale yellow solid (101 mg). This product was dissolved in methylene chloride, and a 1N ethanol solution (360 μ l) of hydrochloric acid. The solvent was distilled off under reduced pressure, a small amount of methanol was added to

20 the residue, and diethyl ether was added dropwise while irradiating with ultrasonic waves to collect precipitate

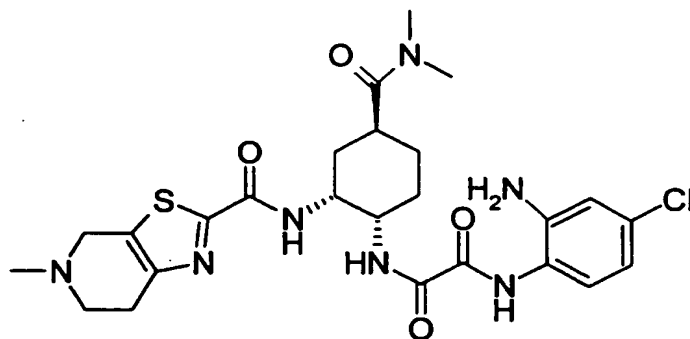
formed. This product was washed with diethyl ether to obtain the title compound (95 mg).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.45-1.53 (1H,m), 1.66-1.73 (3H,m),
1.97-2.10 (2H,m), 2.78 (3H,s), 2.91-2.94 (7H,br.s), 3.11-
5 3.19 (1H,m), 3.29 (1H,br.s), 3.48 (1H,br.s), 3.69 (1H,br.s),
3.95-4.02 (1H,m), 4.44 (2H,br.s), 4.68, 4.72 (1H,each br.s),
4.86 (2.5H,br.s), 6.98 (1H,dd, $J=8.5, 1.9\text{Hz}$), 7.14 (1H,d, $J=8.5\text{Hz}$),
7.35, 7.38 (1H,each br.s), 8.72-8.77 (1H,m), [8.91 (d, $J=7.8\text{Hz}$),
8.99 (d, $J=8.5\text{Hz}$), 1H], 10.45, 10.47 (1H,each br.s),
10 11.74 (1H,br.s).

MS (FAB) m/z : 562 ($\text{M}+\text{H}$) $^+$.

[Example 288]

N^1 -(2-Amino-4-chlorophenyl)- N^2 -((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-
15 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
amino)cyclohexyl)ethanediamide hydrochloride:



The title compound was obtained from the compound
obtained in Example 286 in a similar manner to the process
20 described in Example 287.

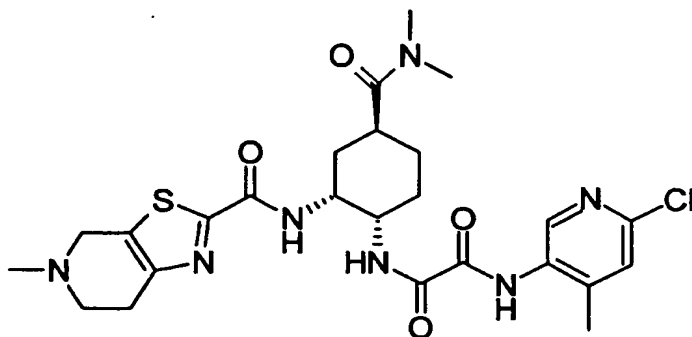
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.45-1.77 (4H,m), 2.06-2.09 (2H,m),

2.78 (3H, s), 2.92 (7H, br. s), 3.12-3.19 (1H, m), 3.26-3.28 (1H, m),
3.48 (1H, br. s), 3.70 (1H, br. s), 4.00-4.44 (5.7H, m),
4.70, 4.74 (1H, each br. s), 6.63-6.66 (1H, m), 6.85 (1H, br. s),
7.18-7.21 (1H, m), 8.77-8.81 (1H, m), [8.97 (d, J=7.8Hz),
5 9.06 (d, J=8.1Hz), 1H], 9.98 (1H, s), 11.60 (1H, br. s).

MS (FAB) m/z: 562 (M+H)⁺.

[Example 289]

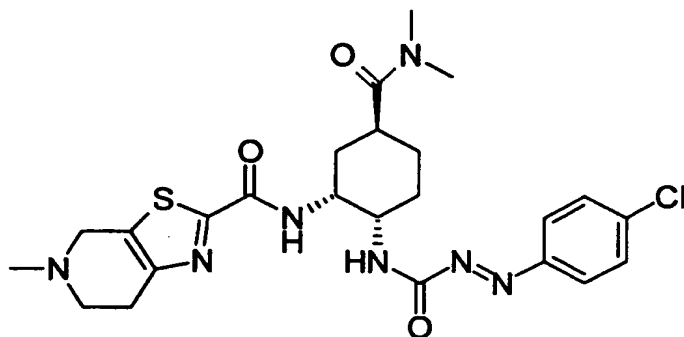
N¹-(6-Chloro-4-methylpyridin-3-yl)-N²-((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-
10 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
amino)cyclohexyl)ethanediamide hydrochloride:



The title compound was obtained by condensing the
compound obtained in Referential Example 270 with the
15 compound obtained in Referential Example 402 and then
treating the condensation product with hydrochloric acid
in a similar manner to the process described Example 199.
¹H-NMR (DMSO-d₆) δ: 1.45-1.54 (1H, m), 1.65-1.77 (3H, m),
2.02-2.08 (2H, m), 2.22 (3H, s), 2.79 (3H, s), 2.89-2.93 (7H, m),
20 3.19 (2H, br. s), 3.54 (2H, br. s), 3.99-4.04 (1H, m), 4.40-
4.42 (1H, m), 4.50 (2H, br. s), 7.49 (1H, s), 8.32 (1H, s),

MS (FAB) m/z : 562 (M+H)⁺.

5 N-{(1R,2S,5S)-2-({[(E)-2-(4-Chlorophenyl)diazenyl]-
carbonyl}amino)-5-[(dimethylamino)carbonyl]cyclohexyl}-5-
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-
carboxamide hydrochloride:

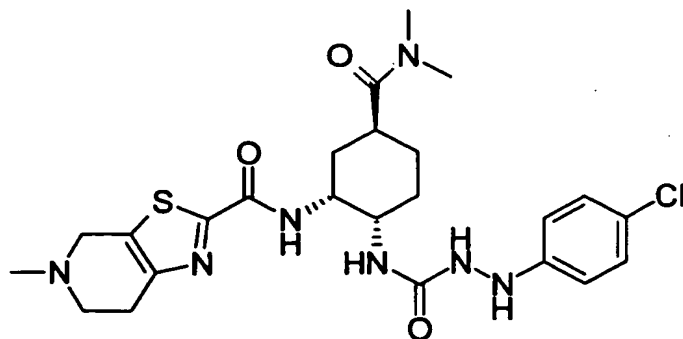


10 After 10% Palladium on carbon (200 mg) was added to a
solution of the compound (700 mg) obtained in Referential
Example 252 in tetrahydrofuran (10 ml), and the mixture
was stirred at room temperature for 2 days under a
hydrogen atmosphere, the reaction mixture was filtered,
15 and the compound obtained in Referential Example 405 (470
mg) was added to a solution of an amine obtained by
concentrating the filtrate in formamide (5.0 ml) to stir
the mixture at 95°C for 18 hours. After the reaction
mixture was concentrated, and a saturated aqueous solution
20 (50 ml) of sodium hydrogencarbonate, water (50 ml) and
methylene chloride (30 ml) were added to conduct liquid

separation, the resultant water layer was extracted with methylene chloride (2 x 20 ml). Organic layers were combined, dried over anhydrous sodium sulfate, concentrated and purified by column chromatography on silica gel (methylene chloride:methanol = 12:1). This purified product was treated with a 1N ethanol solution of hydrochloric acid to obtain the title compound (100 mg).
¹H-NMR (DMSO-d₆) δ: 1.40-1.60 (1H, m), 1.65-2.05 (5H, m), 2.80 (3H, s), 2.91 (3H, s), 2.99 (3H, s), 3.00-3.20 (2H, m), 3.20-3.32 (1H, m), 3.43 (1H, br. s), 3.69 (1H, br. s), 3.95 (1H, br. s), 4.45 (1H, br. s), 4.60-4.80 (2H, m), 7.68 (2H, d, J=8.7 Hz), 7.83 (2H, d, J=8.7 Hz), 8.41 (1H, br. s), 8.68 (1H, d, J=7.6 Hz), 11.40-11.80 (1H, br).
 MS (ESI) m/z: 532 (M+H)⁺.

[Example 291]

N-{(1R,2S,5S)-2-([2-(4-Chlorophenyl)hydrazino]-carbonyl)amino)-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



20

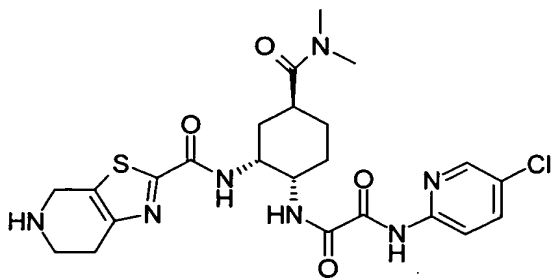
The title compound was obtained by changing the

reaction conditions in the reaction described in Example 290 to conditions that stirring was conducted at 40°C for 3 days.

¹H-NMR (DMSO-d₆) δ: 1.30-1.50 (1H,m), 1.50-1.80 (3H,m),
5 1.80-1.97 (2H,m), 2.76 (3H,s), 2.80-3.05 (2H,m), 2.91 (6H,s),
3.05-3.30 (2H,m), 3.47 (2H,br.s), 4.30-4.50 (2H,m),
4.72 (1H,t, J=12.8Hz), 6.40-6.60 (2H,m), 6.55-6.70 (2H,m),
6.95-7.20 (2H,m), 7.88 (1H,d, J=11.3Hz), 8.48-8.65 (1H,m),
11.48-11.80 (1H,br).
10 MS (ESI) m/z: 534 (M+H)⁺.

[Example 292]

N¹-(5-Chloropyridin-2-yl)-N²-((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[(4,5,6,7-
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
15 amino)cyclohexyl)ethanediamide hydrochloride:



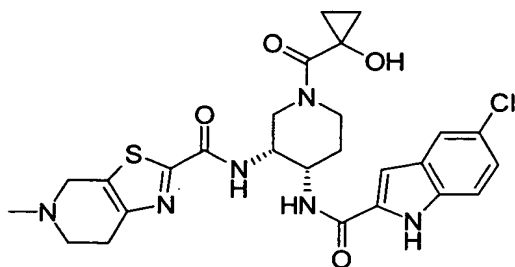
The title compound was obtained by condensing the compound obtained in Referential Example 34 with the compound obtained in Referential Example 420 and then
20 treating the condensation product with hydrochloric acid in a similar manner to the process described Example 17.
¹H-NMR (DMSO-d₆) δ: 1.45-1.55 (1H,m), 1.60-1.80 (3H,m),
1.95-2.10 (2H,m), 2.78 (3H,s), 2.85-3.00 (4H,m),

3.11 (2H, br s), 3.40-3.55 (2H, m), 3.95-4.07 (1H, m), 4.37-
4.45 (1H, m), 4.48 (2H, br s), 8.00-8.01 (2H, m),
8.10 (1H, d, J=7.1 Hz), 8.43-8.47 (1H, m),
9.16 (1H, d, J=7.8 Hz), 9.43 (2H, br s), 10.27 (1H, s).

5 MS (FAB) m/z: 534 (M+H)⁺.

[Example 293]

N-((3R*,4S*)-4-[[(5-Chloroindol-2-yl) carbonyl] amino]-1-
[(1-hydroxycyclopropyl) carbonyl] piperidin-3-yl)-5-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
10 hydrochloride:



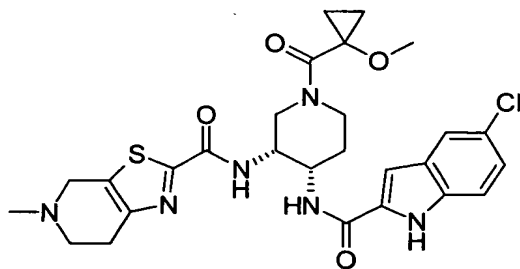
The title compound was obtained by condensing the
compound obtained in Example 118 with 1-hydroxy-1-
cyclopropanecarboxylic acid and then treating the
15 condensation product with hydrochloric acid in a similar
manner to the process described Example 150.

¹H-NMR (DMSO-d₆) δ: 0.60-0.90 (3H, br), 0.92-1.03 (1H, m),
1.71-1.84 (1H, m), 1.85-2.03 (1H, m), 2.91 (3H, s),
3.00-3.80 (7H, m), 4.05-4.80 (5H, m), 6.28-6.42 (1H, br),
20 7.09 (1H, s), 7.18 (1H, dd, J=8.8, 1.5 Hz), 7.42 (1H, d, J=8.8 Hz),
7.70 (1H, d, J=1.5 Hz), 8.14-8.29 (1H, br), 8.41 (1H, br d, J=7.6 Hz),
11.83 (1H, s).

MS (ESI) m/z: 557 (M+H)⁺.

[Example 294]

N-((3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-
[(1-methoxycyclopropyl)carbonyl]piperidin-3-yl)-5-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
5 hydrochloride:

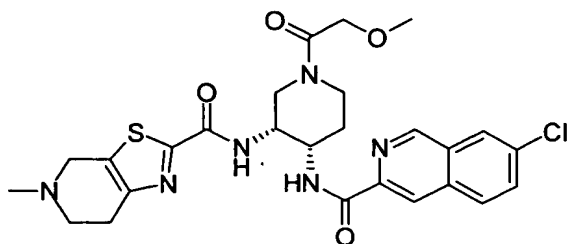


The title compound was obtained by condensing the
compound obtained in Example 118 with the compound
obtained in Referential Example 409 and then treating the
10 condensation product with hydrochloric acid in a similar
manner to the process described Example 150.

¹H-NMR (DMSO-d₆) δ: 0.65-1.05 (4H,m), 1.74-1.88 (1H,m), 1.92-
2.10 (1H,m), 2.91 (3H,s), 3.00-3.80 (10H,m), 4.05-4.83 (6H,m),
7.08 (1H,s), 7.18 (1H,dd, J=8.6, 2.0Hz), 7.42 (1H,d, J=8.6Hz),
15 7.71 (1H,d, J=2.0Hz), 8.08-8.30 (1H,br), 8.41 (1H,br d, J=7.8Hz),
10.60-10.80 (0.5H,br), 10.85-11.05 (0.5H,br), 11.84 (1H,s).

[Example 295]

7-Chloro-N-((3R,4S)-1-(2-methoxyacetyl)-3-{[(5-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-
20 amino}piperidin-4-yl)-3-isoquinolinecarboxamide
hydrochloride:



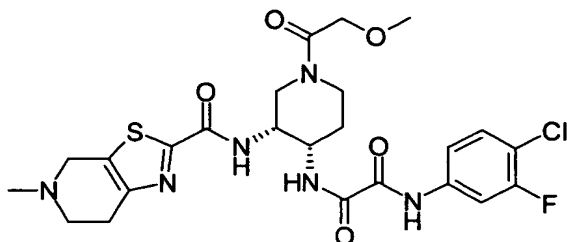
The title compound was obtained by treating the compound obtained in Referential Example 410 with a 4N dioxane solution of hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in Referential Example 10 and then subjecting the condensation product to a hydrochloric acid treatment again in a similar manner to the process described in Example 219.

¹H-NMR (DMSO-d₆) δ: 1.60-1.80 (1H,m), 2.13-2.38 (1H,m), 2.90 (3H,s), 3.00-3.87 (10H,m), 3.89-4.10 (2H,m), 4.15-4.58 (4H,m), 4.60-4.78 (1H,m), 7.89 (1H,d,J=8.8Hz), 8.25 (1H,d,J=8.8Hz), 8.37 (1H,s), 8.61 (1H,s), 8.70-8.95 (1H,m), 9.05-9.29 (1H,m), 9.36 (1H,s), 11.20-11.40 (0.5H,br), 11.45-11.65 (0.5H,br).

MS (ESI) m/z: 557 (M+H)⁺.

[Example 296]

N¹-(4-chloro-3-fluorophenyl)-N²-((3R,4S)-1-(2-methoxyacetyl)-3-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino)piperidin-4-yl)ethanediamide hydrochloride:



The title compound was obtained by treating the compound obtained in Referential Example 411 with a 4N dioxane solution of hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in Referential Example 10 and then subjecting the condensation product to a hydrochloric acid treatment again in a similar manner to the process described in Example 219.

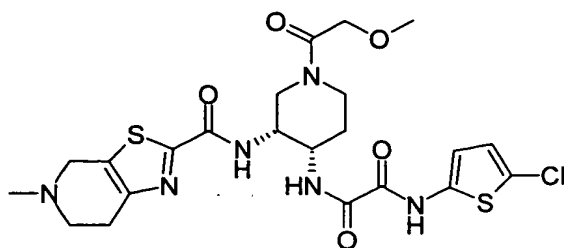
¹H-NMR (DMSO-d₆) δ: 1.60-1.72 (1H,m), 1.98-2.21 (1H,m), 2.91 (3H,s), 3.00-3.52 (9H,m), 3.56-4.05 (3H,m), 4.08-4.50 (4H,m), 4.60-4.78 (1H,br), 7.56 (1H,t, J=8.8Hz), 7.70 (1H,d, J=9.0Hz), 7.91 (1H,dd, J=8.8, 2.3Hz), 8.50-8.72 (1H,m), 9.15-9.35 (1H,m), 11.02 (1H,s), 11.15-11.33 (0.5H,br), 11.35-11.50 (0.5H,br).

MS (FAB) m/z: 567 (M+H)⁺.

[Example 297]

N¹-(5-chloro-2-thienyl)-N²-((3R,4S)-1-(2-methoxyacetyl)-3-(((5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl)amino)piperidin-4-yl)ethanediamide

hydrochloride:



The title compound was obtained by treating the compound obtained in Referential Example 412 with a 4N dioxane solution of hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in Referential Example 10 and then subjecting the condensation product to a hydrochloric acid treatment again in a similar manner to the process described in Example 219.

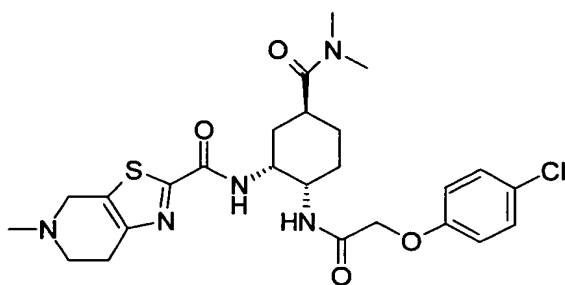
¹H-NMR (DMSO-d₆) δ: 1.60-1.73(1H,m), 1.96-2.19(1H,m), 2.91(3H,s), 3.04-3.54(9H,m), 3.60-4.05(3H,m), 4.07-4.34(3H,m), 4.35-4.54(1H,br), 4.60-4.80(1H,br), 6.89(1H,d,J=4.2Hz), 6.93(1H,d,J=4.2Hz), 8.48-8.70(1H,m), 9.18-9.40(1H,m), 12.31(1H,s).

MS (ESI) m/z: 555(M+H)⁺.

[Example 298]

N-{(1R,2S,5S)-2-{[2-(4-Chlorophenoxy)acetyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide

hydrochloride:



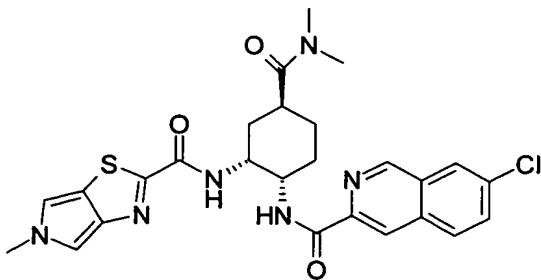
The title compound was obtained by reducing the compound obtained in Referential Example 252, condensing the reduction product with p-chlorophenoxyacetic acid and treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 223.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.35-1.47 (1H, m), 1.55-1.90 (5H, m), 2.77 (3H, s), 2.92 (3H, s), 2.96 (3H, s), 2.98-3.10 (1H, m), 3.10-3.80 (3H, m), 3.85-3.95 (1H, m), 4.35-4.50 (4H, m), 4.50-4.80 (1H, br), 6.85 (2H, d, $J=8.5\text{Hz}$), 7.15-7.35 (1H, br), 7.88-8.03 (1H, br), 8.46 (1H, d, $J=8.8\text{Hz}$), 11.30-11.65 (1H, br).

MS (FAB) m/z : 534 ($\text{M}+\text{H}$) $^+$.

[Example 299]

7-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[(5-methyl-5H-pyrrolo[3,4-d]thiazol-2-yl)carbonyl]amino)-cyclohexyl)-3-isoquinolinecarboxamide hydrochloride:



The title compound was obtained by condensing the

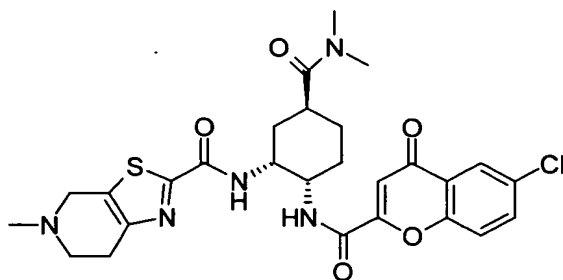
lithium salt of the carboxylic acid obtained by hydrolyzing the compound obtained in Referential Example 413 with a compound obtained by deprotecting the the compound obtained in Referential Example 146 by an acid treatment and treating the condensation product with hydrochloric acid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.00-1.11 (2H, m), 1.45-1.60 (1H, m), 1.65-1.85 (1H, m), 1.95-2.06 (1H, m), 2.10-2.24 (1H, m), 2.78 (3H, s), 2.87-3.02 (1H, m), 2.94 (3H, s), 3.88 (3H, s), 4.16-4.27 (1H, m), 4.45-4.56 (1H, m), 7.03 (1H, s), 7.55 (1H, s), 7.87 (1H, br d, $J=8.3\text{Hz}$), 8.24 (1H, br d, $J=8.8\text{Hz}$), 8.33 (1H, s), 8.59 (1H, s), 8.85 (1H, br d, $J=7.6\text{Hz}$), 9.01 (1H, br d, $J=7.8\text{Hz}$), 9.28 (1H, s).

MS (ESI) m/z : 539 ($\text{M}+\text{H}$) $^+$.

[Example 300]

N-((1R,2S,5S)-2-(((6-Chloro-4-oxo-4H-chromen-2-yl)-carbonyl)amino))-5-((dimethylamino)carbonyl)cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



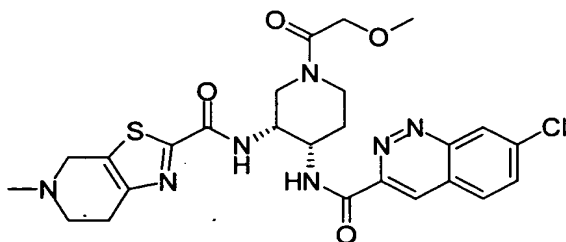
The title compound was obtained by condensing a compound obtained by treating the compound in Referential Example 417 with a 4N dioxane solution of hydrochloric

acid with the compound obtained in Referential Example 10 and then treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 219.

5 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.40-1.53 (1H,m), 1.67-2.04 (5H,m),
2.40-2.53 (1H,m), 2.80 (3H,s), 2.92 (3H,s), 3.01 (3H,s),
3.09-3.22 (3H,m), 3.66-3.77 (1H,m), 4.01-4.10 (1H,m),
4.34-4.49 (1H,m), 4.58-4.76 (2H,m), 6.80 (1H,d, $J=4.9\text{Hz}$),
7.59-7.70 (1H,m), 7.90-8.00 (1H,m), 7.96 (1H,s), 8.52-8.60 (1H,m),
10 8.80-8.90 (1H,m), 11.10-11.25 (0.5H,br), 11.40-11.55 (0.5H,br).
MS (ESI) m/z : 572 ($\text{M}+\text{H}$) $^+$.

[Example 301]

7-Chloro-N-((3R,4S)-1-(2-methoxyacetyl)-3-{[(5-methyl-
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-
15 carbonyl]amino}piperidin-4-yl)-3-cinnolinecarboxamide
hydrochloride:



The title compound was obtained by condensing a compound obtained by treating the compound obtained in Referential Example 418 with a 4N dioxane solution of hydrochloric acid with the compound obtained in Referential Example 10 and then treating the condensation product with hydrochloric acid in a similar manner to the

20

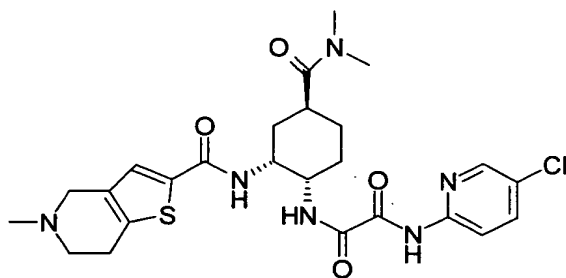
process described in Example 219.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.70-1.80 (1H, m), 1.85-2.05 (1H, m),
2.90 (3H, s), 3.00-3.20 (2H, m), 3.16 (3H, s), 3.22-3.82 (7H, m),
3.88-4.80 (5H, m), 7.09 (1H, d, $J=9.0\text{Hz}$), 7.17 (1H, dd, $J=8.8, 1.9\text{Hz}$),
5 7.42 (1H, d, $J=8.8\text{Hz}$), 7.70 (1H, d, $J=1.9\text{Hz}$), 8.29 (1H, br s),
8.40-8.50 (1H, m), 11.20-11.50 (1H, br m), 11.85 (1H, s).

MS (ESI) m/z : 558 ($\text{M}+\text{H}$) $^+$.

[Example 302]

N^1 -(5-Chloropyridin-2-yl)- N^2 -((1S, 2R, 4S)-4-
10 [(dimethylamino)carbonyl]-2-[[5-methyl-4, 5, 6, 7-
tetrahydrothieno[3, 2-c]pyridin-2-yl)carbonyl]amino}-
cyclohexyl)ethanediamide hydrochloride:



The title compound was obtained by deprotecting the
15 compound obtained in Referential Example 421 with
hydrochloric acid, methylating the deprotected compound in
a similar manner to the process described in Example 18
and treating it with hydrochloric acid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.42-1.58 (1H, m), 1.59-1.80 (3H, m),
20 1.83-1.95 (1H, m), 1.97-2.10 (1H, m), 2.78 (3H, s), 2.89 (3H, s),
2.96 (3H, s), 3.00-3.10 (1H, m), 3.10-3.20 (2H, m),
3.45-3.80 (1H, m), 3.90-4.00 (2H, m), 4.00-4.50 (3H, m),
7.77 (1H, s), 7.95-8.05 (3H, m), 8.44 (1H, t, $J=1.6\text{Hz}$),

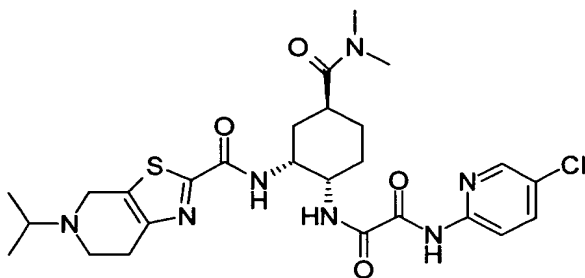
8.90 (1H, d, J=8.6Hz), 10.25 (1H, s), 11.12 (1H, br s).

MS (ESI) m/z: 547 (M+H)⁺.

[Example 303]

N¹-(5-Chloropyridin-2-yl)-N²-((1S,2R,4S)-4-

5 [(dimethylamino)carbonyl]-2-[[(5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino-cyclohexyl)ethanediamide hydrochloride:



The title compound was obtained by condensing the
10 compound obtained in Referential Example 418 with the
compound obtained in Referential Example 420 and then
treating the condensation product with hydrochloric acid
in a similar manner to the process described in Example 2.

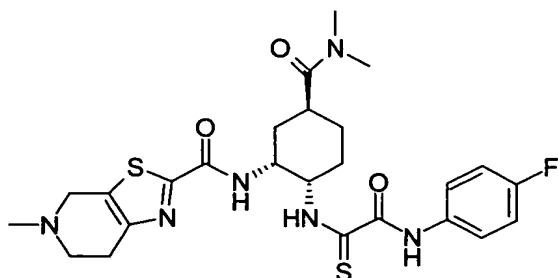
¹H-NMR (DMSO-d₆) δ: 1.30-1.40 (6H, m), 1.38-1.58 (1H, m),
15 1.59-1.82 (3H, m), 1.95-2.13 (2H, m), 2.40-2.65 (1H, m), 2.49 (3H, s),
2.87-3.55 (4H, m), 2.49 (3H, s), 3.60-3.82 (2H, m), 3.93-4.04 (1H, m),
4.37-4.55 (2H, m), 4.55-4.72 (1H, m), 7.94-8.10 (2H, m), 8.43 (1H, s),
8.64-8.77 (1H, m), 9.12 (1/2H, d, J=7.8Hz), 9.24 (1/2H, d, J=7.8Hz),
10.22 (1/2H, s), 10.26 (1/2H, s), 11.25 (1/2H, br s),
20 11.44 (1/2H, br s).

MS (FAB) m/z: 578 (M+H)⁺.

[Example 304]

N-((1R,2S,5S)-5-[(Dimethylamino)carbonyl]-2-[[2-(4-

fluoroanilino)-2-oxoethanethioyl]amino)cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



5 The title compound was obtained by treating the compound obtained in Referential Example 424 with hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in Referential Example 10 and then subjecting the
10 condensation product to a hydrochloric acid treatment again in a similar manner to the process described in Example 219.

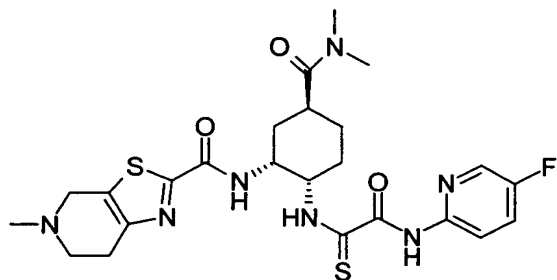
¹H-NMR (DMSO-d₆) δ: 1.45-1.60 (1H,m), 1.60-1.80 (3H,m), 2.00-2.10 (1H,m), 2.20-2.35 (1H,m), 2.79 (3H,s), 2.93 (3H,s),
15 2.95 (3H,s), 2.95-3.10 (1H,m), 3.10-3.30 (2H,m), 3.40-3.60 (1H,m), 3.60-3.80 (1H,m), 4.35-4.50 (1H,m), 4.50-4.60 (1H,m), 4.60-4.80 (2H,m), 7.20 (2H,t, J=8.8Hz), 7.77 (2H,dd, J=9.0, 5.1Hz), 8.80 (1H,br), 10.42 (1H,s), 10.93 (1H,br), 11.28 (1H,br).

20 MS (ESI) m/z: 547 (M+H)⁺.

[Example 305]

N-[(1R,2S,5S)-5-[(Dimethylamino)carbonyl]-2-({2-[(5-fluoropyridin-2-yl)amino]-2-oxoethanethioyl}amino)-

cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridine-2-carboxamide hydrochloride:



The title compound was obtained by treating the
5 compound obtained in Referential Example 427 with
hydrochloric acid to deprotect it, condensing the
deprotected compound with the compound obtained in
Referential Example 10 and then subjecting the
condensation product to a hydrochloric acid treatment
10 again in a similar manner to the process described in
Example 219.

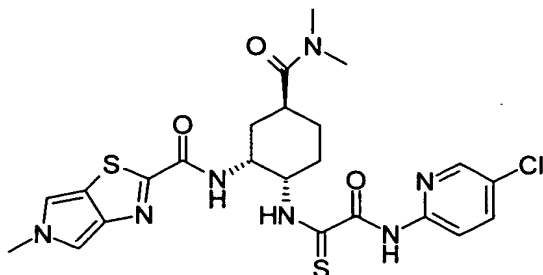
$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.43-1.57 (1H,m), 1.64-1.87 (3H,m),
2.00 (1H,br s), 2.17-2.34 (1H,m), 2.78 (3H,s), 2.90 (3H,s),
2.95 (3H,s), 2.95-3.10 (1H,m), 3.10-3.30 (2H,m), 3.40-
15 3.60 (1H,m), 3.68 (1H,br s), 4.44 (1H,br s), 4.45-
4.56 (1H,m), 4.60-4.73 (2H,m), 7.80-
7.90 (1H,m), 8.08 (1H,dd, $J=9.1, 3.9\text{Hz}$),
8.41 (1H,d, $J=2.9\text{Hz}$), 8.79 (1H,d, $J=6.6\text{Hz}$), 10.49 (1H,s),
11.07 (1H,br s), 11.69 (1H,br).

20 MS (ESI) m/z : 548 ($\text{M}+\text{H}$) $^+$.

[Example 306]

N-((1R,2S,5S)-2-((2-((5-Chloropyridin-2-yl)amino)-2-
oxoethanethioyl)amino)-5-((dimethylamino)carbonyl)-

cyclohexyl)-5-methyl-5H-pyrrolo[3,4-d]thiazole-2-carboxamide:



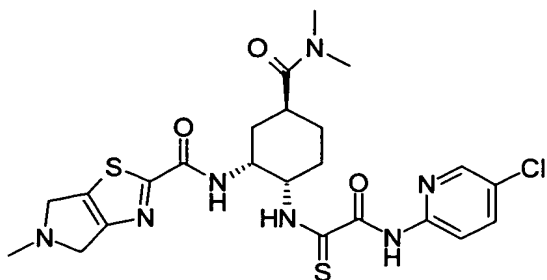
The title compound was obtained by treating the
5 compound obtained in Referential Example 428 with
hydrochloric acid to deprotect it and then condensing the
deprotected compound with the compound obtained in
Referential Example 293 in a similar manner to the process
described in Example 219.

10 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.45-1.58 (1H,m), 1.63-1.73 (2H,m), 1.73-
1.87 (2H,m), 2.00-2.10 (1H,m), 2.20-2.35 (1H,m), 2.79 (3H,s),
2.95 (3H,s), 2.96-3.10 (1H,m), 3.89 (3H,s), 4.48-
4.58 (1H,m), 4.60-4.70 (1H,m), 7.05 (1H,d, $J=1.7\text{Hz}$),
7.55 (1H,d, $J=1.7\text{Hz}$), 8.00 (1H,dd, $J=8.9, 2.4\text{Hz}$),
15 8.05 (1H,d, $J=8.9\text{Hz}$), 8.44 (1H,d, $J=2.4\text{Hz}$), 8.71 (1H,d, $J=7.3\text{Hz}$),
10.57 (1H,s), 11.13 (1H,d, $J=7.8\text{Hz}$).

MS (FAB) m/z : 548 ($\text{M}+\text{H}$) $^+$.

[Example 307]

N-((1R,2S,5S)-2-((2-((5-Chloropyridin-2-yl)amino)-2-
20 oxoethanethioyl)amino)-5-[(dimethylamino)carbonyl]-
cyclohexyl)-5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]-
thiazole-2-carboxamide hydrochloride:



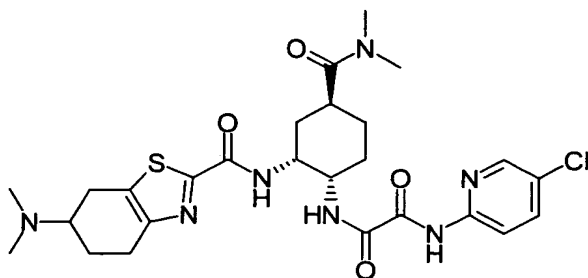
The title compound was obtained by treating the compound obtained in Referential Example 428 with hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in Referential Example 293 under an argon atmosphere and then subjecting the condensation product to a hydrochloric acid treatment again in a similar manner to the process described in Example 219.

¹H-NMR (DMSO-d₆) δ: 1.42-1.58 (1H, m), 1.65-1.87 (3H, m), 1.97-2.10 (1H, m), 2.17-2.30 (1H, m), 2.80 (3H, s), 2.96 (3H, s), 2.98-3.10 (1H, m), 3.07 (3H, s), 4.30-5.00 (6H, m), 8.00-8.10 (1H, m), 8.46 (1H, d, J=2.4 Hz), 8.79 (1H, t, J=7.3 Hz), 10.54 (1H, s), 11.04 (1H, d, J=7.8 Hz), 12.24 (1H, br s).

MS (ESI) m/z: 550 (M+H)⁺.

[Example 308]

N¹-(5-Chloropyridin-2-yl)-N²-[(1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-({[6-(dimethylamino)-4,5,6,7-tetrahydrobenzothiazol-2-yl]carbonyl}amino)cyclohexyl]-ethanediamide:



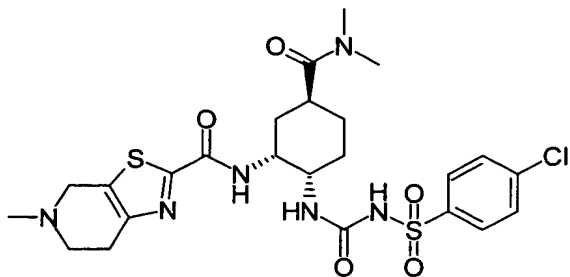
The title compound was obtained by deprotecting the compound obtained in Referential Example 431 with hydrochloric acid, methylating the deprotected compound in a similar manner to the process described in Example 18 and treating it with hydrochloric acid.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.42-1.58 (1H, m), 1.59-1.80 (3H, m), 1.90-2.12 (3H, m), 2.30-2.45 (1H, m), 2.70-3.00 (11H, m), 2.92 (3H, s), 3.00-3.20 (2H, m), 3.25-3.45 (1H, m), 3.63-3.80 (1H, m), 3.88-4.02 (1H, m), 4.35-4.47 (1H, m), 8.02 (1H, s), 8.42-8.55 (1H, m), 8.60-8.68 (1H, m), 8.93 (1H, dd, $J=14.5, 8.2\text{Hz}$), 9.19 (1H, dd, $J=17.7, 8.2\text{Hz}$), 10.28 (1H, s), 10.91 (1H, br s).

MS (ESI) m/z : 576 ($\text{M}+\text{H}$) $^+$.

[Example 309]

N-{(1R,2S,5S)-2-[(4-Chlorophenyl)sulfonyl]amino}-carbonyl)amino]-5[(dimethylamino)carbonyl]cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



4-Chlorophenylsulfonyl isocyanate (148 μ l) was added to a solution of the compound (328.0 mg) obtained in Referential Example 253 in methylene chloride (10 ml), and the mixture was stirred at room temperature for 24 hours.

5 The solvent was distilled off under reduced pressure, and residue was purified by preparative thin-layer column chromatography on silica gel (methylene chloride:methanol = 9:1). The thus-obtained product was dissolved in ethanol (2 ml) and methylene chloride (2 ml), and a 1N ethanol

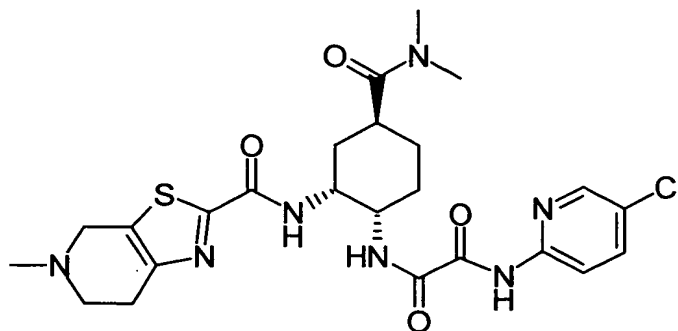
10 solution (0.25 ml) of hydrochloric acid was added to stir the mixture at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was solidified with diethyl ether to obtain the title compound (104.3 mg).

15 $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.25-1.45 (1H,m), 1.45-1.80 (5H,m), 2.76 (3H,s), 2.94 (3H,s), 2.97 (3H,s), 3.00-3.80 (6H,m), 4.35-4.85 (3H,m), 6.53 (1H,brs), 7.66 (2H,d, $J=8.5\text{Hz}$), 7.86 (2H,d, $J=8.5\text{Hz}$), 8.50-8.82 (1H,m), 10.64 (1H,br s), 11.10-11.80 (1H,br).

20 MS (ESI) m/z : 583 ($\text{M}+\text{H}$) $^+$.

[Example 310]

N^1 -(5-Chloropyridin-2-yl)- N^2 -((1S,2R,4S)-4-
 [(dimethylamino)carbonyl]-2-[[(5-methyl-4,5,6,7-
 tetrahydrothiazolo[5,4-c]pyridin-2-
 25 yl)carbonyl]amino)cyclohexyl)ethanediamide:



The compound (6.2 g) obtained in Example 310 is dissolved in methylene chloride (120 ml), a 1 mol/L ethanol solution (11.28 ml) of p-toluenesulfonic acid was added to the solution, and the solvent was distilled off. Ethanol (95 ml) containing 15% water was added to the residue, and the mixture was stirred at 60°C to dissolve it. The solution was then cooled to room temperature and stirred for a day. Crystals deposited were collected by filtration, washed with ethanol and dried at room temperature for 2 hours under reduced pressure to obtain the title compound (7.4 g).

¹H-NMR (DMSO-d₆) δ: 1.45-1.54 (1H, m), 1.66-1.78 (3H, m), 2.03-2.10 (2H, m), 2.28 (3H, s), 2.79 (3H, s), 2.91-3.02 (1H, m), 2.93 (3H, s), 2.99 (3H, s), 3.13-3.24 (2H, m), 3.46-3.82 (2H, m), 3.98-4.04 (1H, m), 4.43-4.80 (3H, m), 7.11 (2H, d, J=7.8 Hz), 7.46 (2H, d, J=8.2 Hz), 8.01 (2H, d, J=1.8 Hz), 8.46 (1H, t, J=1.8 Hz), 8.75 (1H, d, J=6.9 Hz), 9.10-9.28 (1H, br), 10.18 (1H, br), 10.29 (1H, s).

MS (ESI) m/z: 548 (M+H)⁺.

Elemental analysis: C₂₄H₃₀ClN₇O₄S·C₇H₈O₃S·H₂O.

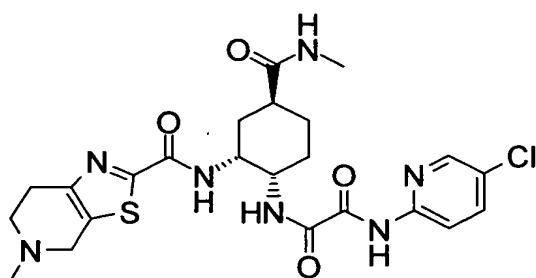
Calculated: C; 50.43, H; 5.46, N; 13.28, Cl; 4.80, S; 8.69.

Found: C;50.25,H;5.36,N;13.32,Cl;4.93,S;8.79.

mp(decomposed): 245~248°C.

[Example 312]

N¹-(5-Chloropyridin-2-yl)-N²-((1S,2R,4S)-4-[(methylamino)-
5 carbonyl]-2-[[(5-methyl-4,5,6,7-tetrahydrothiazoro[5,4-c]-
pyridin-2-yl) carbonyl] amino} cyclohexyl) ethanediamide
hydrochloride:



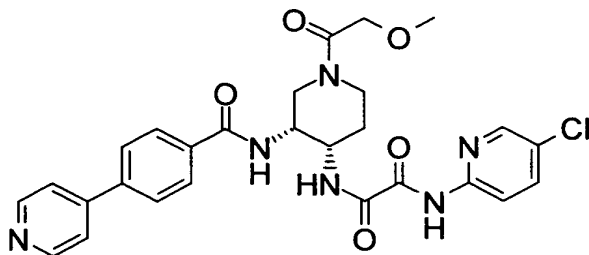
The title compound was obtained by treating the
10 compound obtained in Referential Example 437 with
hydrochloric acid to deprotect it, condensing the
deprotected compound with the compound obtained in
Referential Example 10 and then treating the condensation
product with hydrochloric acid again in a similar manner
15 to the process described in Example 219.

¹H-NMR (DMSO-d₆) δ: 1.48-1.61(1H,m), 1.61-1.74(2H,m), 1.74-
1.82(1H,m), 1.98-2.12(2H,m), 2.29-2.38(1H,m),
2.53(3H,d,J=4.2Hz), 2.92(3H,s), 3.10-3.40(4H,br), 3.40-
3.80(1H,br), 3.97-4.05(1H,m), 4.28-4.34(1H,m), 4.34-
20 4.80(1H,br), 7.70-7.78(1H,m), 7.97-8.07(2H,m), 8.43-
8.50(1H,m), 8.49(1H,br.s), 9.27(1H,d,J=7.8Hz),
10.26(1H,br.s), 11.48(1H,br.s).

MS (ESI) m/z: 534[(M+H)⁺,Cl³⁵], 535[(M+H)⁺,Cl³⁷].

[Example 313]

N¹-(5-Chloropyridin-2-yl)-N²-((3R,4S)-1-(2-methoxyacetyl)-3-([4-(pyridin-4-yl)benzoyl]amino)piperidin-4-yl)ethanediamide hydrochloride:



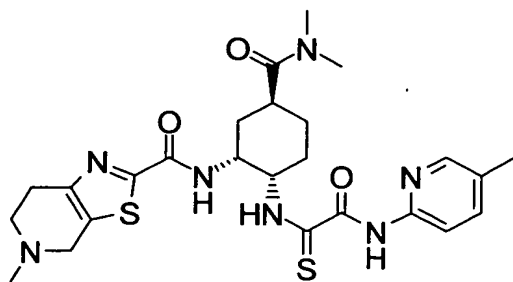
The title compound was obtained by treating the compound obtained in Referential Example 368 with a 4N dioxane solution of hydrochloric acid to deprotect it, condensing the deprotected compound with the compound
10 obtained in Referential Example 237 and then treating the condensation product with hydrochloric acid again in a similar manner to the process described in Example 219.
¹H-NMR (DMSO-d₆) δ: 1.62-1.75(1H,m), 2.00-2.20(1H,m), 2.80-4.40(11H,m), 7.90-8.00(4H,m), 8.05-8.13(2H,m), 8.14-
15 8.43(3H,m), 8.40-8.45(1H,m), 8.87-9.04(3H,m), 10.20-10.50(2H,br).

MS (FAB) m/z: 551[(M+H)⁺,Cl³⁵], 553[(M+H)⁺,Cl³⁷].

[Example 314]

N-((1R,2S,5S)-5-[(Dimethylamino)carbonyl]-2-({2-[(5-methylpyridin-2-yl)amino]-2-oxoethanethioyl}amino)-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-carboxamide hydrochloride:

20



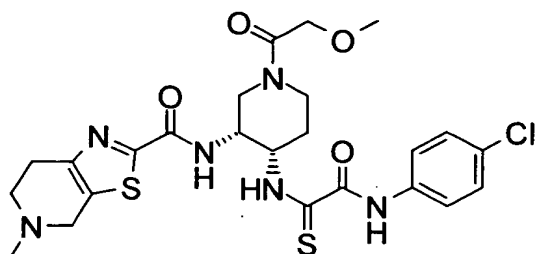
The title compound was obtained by treating the compound obtained in Referential Example 440 with hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in Referential Example 10 and then treating the condensation product with hydrochloric acid again in a similar manner to the process described in Example 219.

¹H-NMR (DMSO-d₆) δ: 1.45-1.60 (1H,m), 1.65-1.90 (3H,m), 2.00-2.10 (1H,m), 2.20-2.40 (1H,m), 2.28 (3H,s), 2.80 (3H,s), 2.91 (3H,s), 2.95-3.10 (1H,m), 2.96 (3H,s), 3.15-3.30 (1H,m), 3.32 (2H,s), 3.50-3.80 (1H,m), 4.45-4.60 (2H,m), 4.60-4.80 (2H,m), 7.72 (1H,d,J=8.5Hz), 7.97 (1H,d,J=8.5Hz), 8.23 (1H,s), 8.83 (1H,d,J=7.3Hz), 10.38 (1H,s), 11.06 (1H,d,J=7.6Hz), 11.49 (1H,br.s).

MS (ESI) m/z: 544 (M+H)⁺.

[Example 315]

N-[(3R,4S)-4-{[2-(4-Chloroanilino)-2-oxoethanethioyl]-amino}-1-(2-methoxyacetyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-carboxamide hydrochloride:



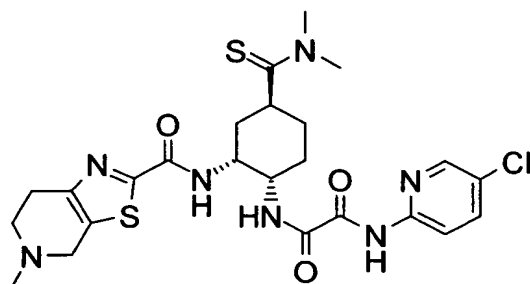
The title compound was obtained by treating the compound obtained in Referential Example 441 with hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in Referential Example 10 and then treating the condensation product with hydrochloric acid again in a similar manner to the process described in Example 219.

¹H-NMR (DMSO-d₆) δ: 1.71-1.82 (1H,m), 2.18-2.44 (1H,m), 2.89 (3H,s), 3.00-4.85 (17H,m), 7.41 (2H,d,J=8.8Hz), 7.77 (2H,d,J=8.8Hz), 8.48-8.73 (1H,m), 10.48 (1H,br.s), 10.90-11.06 (1H,m), 11.45-11.90 (1H,br).

MS (ESI) m/z: 565 [(M+H)⁺,Cl³⁵], 567 [(M+H)⁺,Cl³⁷].

[Example 316]

N¹-(5-Chloropyridin-2-yl)-N²-((1S,2R,4S)-4-[(dimethylamino)carbothioyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino)-cyclohexyl)ethanediamide hydrochloride:



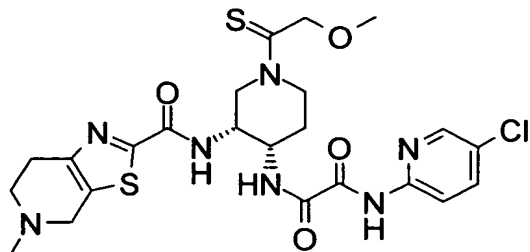
The title compound was obtained by condensing the compound obtained in Referential Example 445 with the compound obtained in Referential Example 10 and treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 3.

¹H-NMR (DMSO-d₆) δ: 1.66-2.15 (6H,m), 2.93 (3H,s), 3.15-3.40 (9H,m), 3.49 (1H,br.s), 3.71 (1H,br.s), 3.97-4.01 (1H,m), 4.42 (2H,br.s), 4.70 (1H,br.s), 8.01 (2H,br.s), 8.46 (1H,br.s), 8.78 (1H,d,J=6.8Hz), 9.24 (1H,br.s), 10.28 (1H,s), 11.29 (1H,br.s).

MS (FAB) m/z: 564 [(M+H)⁺,Cl³⁵], 566 [(M+H)⁺,Cl³⁷].

[Example 317]

N¹-(5-Chloropyridin-2-yl)-N²-((3R,4S)-1-(2-methoxyethanethieryl)-3-[[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino]-piperidin-4-yl)ethanediamide hydrochloride:



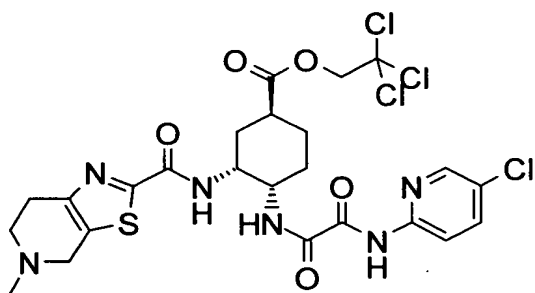
The title compound was obtained by treating the compound obtained in Referential Example 448 with hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in Referential Example 10 and then treating the condensation product with hydrochloric acid again in a similar manner to the process described in Example 219.

¹H-NMR (DMSO-d₆) δ: 1.74-1.85(1H,m), 2.13-2.35(1H,m), 2.89(3H,s), 2.95-3.98(9H,m), 4.05-5.33(8H,m), 7.95-8.06(2H,m), 8.43(1H,s), 8.48-8.73(1H,br), 9.29-9.45(1H,br), 10.21-10.34(1H,br), 11.45-11.90(1H,br).

MS (ESI) m/z: 566[(M+H)⁺,Cl³⁵], 568[(M+H)⁺,Cl³⁷].

[Example 318]

2,2,2-Trichloroethyl (1S,3R,4S)-4-({2-[(5-Chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-cyclohexanecarboxylate:



The title compound was obtained by treating the compound obtained in Referential Example 453 with hydrochloric acid to deprotect it, condensing the deprotected compound with the compound obtained in

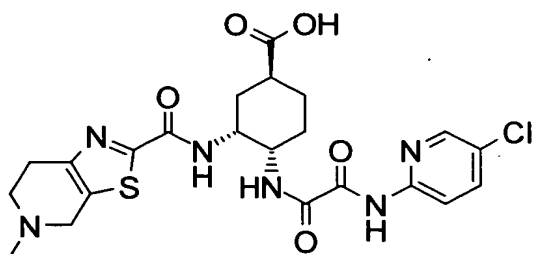
Referential Example 10 and then treating the condensation product with hydrochloric acid again in a similar manner to the process described in Example 219.

¹H-NMR (CDCl₃) δ: 1.60-1.87 (2H,m), 2.04-2.15 (2H,m), 2.21-2.32 (2H,m), 2.52 (3H,s), 2.73-2.89 (3H,m), 2.92-2.98 (2H,m), 3.71 (1H,d,J=15.4Hz), 3.73 (1H,d,J=15.4Hz), 4.08-4.16 (1H,m), 4.66-4.71 (1H,m), 4.72 (1H,d,J=12.0Hz), 4.82 (1H,d,J=12.0Hz), 7.37 (1H,d,J=8.8Hz), 7.69 (1H,dd,J=8.8,2.4Hz), 8.05 (1H,d,J=8.1Hz), 8.16 (1H,d,J=8.8Hz), 8.30 (1H,d,J=2.4Hz), 9.69 (1H,s).

MS (ESI) m/z: 651 [(M+H)⁺, 3xCl³⁵], 653 [(M+H)⁺, 2xCl³⁵, Cl³⁷], 655 [(M+H)⁺, Cl³⁵, 2xCl³⁷].

[Example 319]

(1S,3R,4S)-4-({2-[5-Chloropyridin-2-yl]amino}-2-oxoacetyl)amino)-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-cyclohexane carboxylic acid:



The compound (475 mg) obtained in Example 318 was dissolved in tetrahydrofuran (50 ml), zinc (2.85 g) and acetic acid (5.7 ml) were successively added to the solution, and the mixture was stirred at room temperature for 3 hours. Celite 545 (2.85 g) was added to the reaction

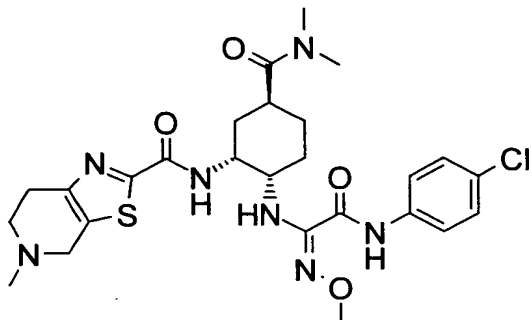
mixture to remove insoluble matter by filtration. After the filtrate was concentrated under reduced pressure, methylene chloride was added to the resultant residue, and a 1N aqueous solution of sodium hydroxide was added with stirring to adjust the pH of the reaction mixture to 7. After an organic layer was separated, saturated saline (50 ml) was added to a water layer to conduct extraction with methylene chloride. The resultant organic layers were combined and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 95:5 → 9:1 → 4:1) to obtain the title compound (140 mg).

¹H-NMR (DMSO-d₆) δ: 1.50-1.80(3H,m), 1.84-1.95(1H,m), 1.95-2.10(1H,m), 2.15-2.30(1H,m), 2.38(3H,s), 2.40-2.50(1H,m), 2.67-2.80(2H,m), 2.80-2.95(2H,m), 3.66(2H,m), 4.03(1H,br.s), 4.33(1H,br.s), 7.97-8.10(2H,m), 8.45(1H,s), 8.53(1H,d,J=6.8Hz), 9.19(1H,d,J=8.3Hz), 10.27(1H,br.s).

MS (FAB) m/z: 521[(M+H)⁺, ³⁵Cl], 523[(M+H)⁺, ³⁷Cl].

[Example 320]

N-{(1R,2S,5S)-2-{[2-(4-Chloroanilino)-1-methoxyimino-2-oxoethyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-carboxamide hydrochloride:



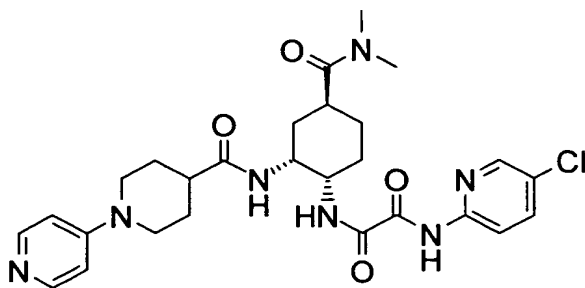
The title compound was obtained by hydrolyzing an ester of the compound obtained in Referential Example 454 in a similar manner to the process described in Example 142, condensing the hydrolyzate with 4-chloroaniline in a similar manner to the process described in Referential Example 143 and then treating the condensation product with hydrochloric acid.

¹H-NMR (DMSO-d₆) δ: 1.30-1.17(1H,m), 1.50-1.62(1H,m), 1.62-1.75(2H,m), 1.85-2.00(2H,m), 2.76(3H,s), 2.93(6H,br.s), 3.00-3.10(1H,m), 3.18(1H,br.s), 3.27(1H,br.s), 3.49(1H,br.s), 3.71(1H,br.s), 3.76(3H,s), 3.93(1H,br.s), 4.35-4.50(2H,m), 4.66-4.77(1H,m), 6.09(0.5H,d,J=7.8Hz), 6.19(0.5H,d,J=7.8Hz), 7.38(2H,d,J=8.8Hz), 7.71(2H,d,J=8.8Hz), 8.70-8.79(1H,m), 10.28(1H,d,J=11.0Hz), 11.53(0.5H,br.s), 11.45(0.5H,br.s).

MS (FAB) m/z: 576[(M+H)⁺,³⁵Cl], 578[(M+H)⁺,³⁷Cl].

[Example 321]

N¹-(5-Chloropyridin-2-yl)-N²-[(1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-({[1-(pyridin-4-yl)piperidin-4-yl]carbonyl}amino)cyclohexyl]ethanediamide hydrochloride:



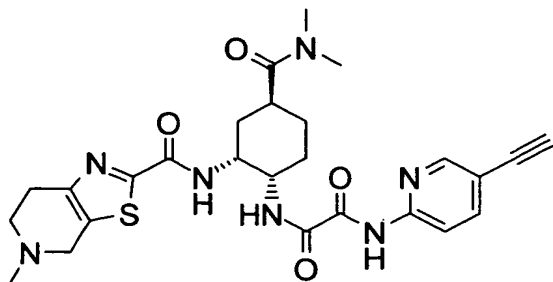
The title compound was obtained by condensing the compound obtained in Referential Example 420 with 1-(pyridin-4-yl)piperidine-4-carboxylic acid (w096/10022) and treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 2.

¹H-NMR (DMSO-d₆) δ: 1.35-1.49 (1H, m), 1.49-1.78 (6H, m), 1.78-1.98 (3H, m), 2.75-2.90 (1H, m), 2.78 (3H, s), 3.02 (3H, s), 3.03-3.14 (1H, m), 3.14-3.28 (2H, m), 3.74-3.85 (1H, m), 4.13-4.30 (3H, m), 7.18 (2H, d, J=7.3Hz), 7.99 (2H, s), 8.10-8.23 (3H, m), 8.41 (1H, s), 8.50 (1H, d, J=8.1Hz), 10.19 (1H, s), 13.73 (1H, br. s).

MS (FAB) m/z: 556[(M+H)⁺, ³⁵Cl], 558[(M+H)⁺, ³⁷Cl].

[Example 322]

N¹-((1S,2R,4S)-4-[(Dimethylamino)carbonyl]-2-[[5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-amino)cyclohexyl)-N²-(5-ethynylpyridin-2-yl)ethanediamide:

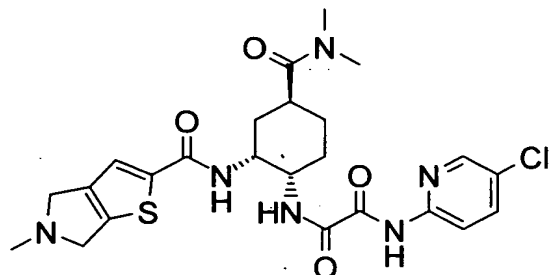


The compound (348 mg) obtained in Referential Example 455 was dissolved in tetrahydrofuran (14 ml), tetrabutylammonium fluoride (1N tetrahydrofuran solution, 628 μ l) was added to the solution, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was decolorized with activated carbon (about 1 g) and dried over anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 93:7) and then dissolved in methylene chloride (about 1 ml). Hexane (about 10 ml) was added to the solution, and precipitate formed was collected by filtration to obtain the title compound (116 mg).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.62-2.14 (8H, m), 2.52 (3H, s), 2.79-2.95 (6H, m), 3.05 (3H, s), 3.19 (1H, s), [AB pattern 3.71 (1H, d, $J=15.5\text{Hz}$), 3.74 (1H, d, $J=15.5\text{Hz}$)], 4.08-4.14 (1H, m), 4.66-4.69 (1H, m), 7.41 (1H, d, $J=8.6\text{Hz}$), 7.80 (1H, dd, $J=8.6, 2.2\text{Hz}$), 8.03 (1H, d, $J=7.6\text{Hz}$), 8.15 (1H, d, $J=8.6\text{Hz}$), 8.46 (1H, d, $J=2.2\text{Hz}$), 9.75 (1H, s).
MS (ESI) m/z : 538 ($\text{M}+\text{H}$) $^+$.

[Example 323]

N¹-(5-Chloropyridin-2-yl)-N²-((1S,2R,4S)-4-
[(dimethylamino)carbonyl]-2-[[(5-methyl-5,6-dihydro-4H-
thieno[2,3-c]pyrrol-2-yl)carbonyl]amino)cyclohexyl)-
5 ethanediamide:



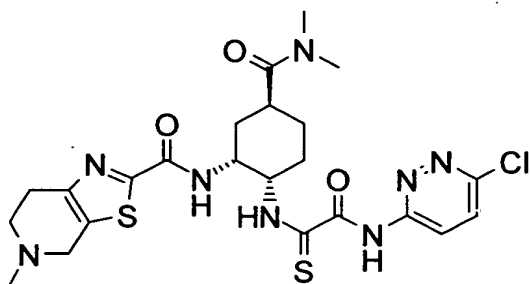
The title compound was obtained by hydrolyzing the
compound obtained in Referential Example 456 and
condensing the hydrolyzate with the compound obtained in
10 Referential Example 420 in a similar manner to the process
described in Example 191.

¹H-NMR (CDCl₃) δ: 1.80-2.15(6H,m), 2.64(3H,s), 2.76-
2.79(1H,m), 2.94(3H,s), 3.03(3H,s), 3.84-3.86(2H,m), 3.94-
3.99(3H,m), 4.58-4.59(1H,m), 6.70(1H,d,J=6.3Hz),
15 7.31(1H,s), 7.70(1H,dd,J=8.8,2.3Hz), 8.15-8.18(2H,m),
8.30(1H,d,J=2.3Hz), 9.72(1H,br.s).

MS (FAB) m/z: 533[(M+H)⁺,Cl³⁵], 535[(M+H)⁺,Cl³⁷].

[Example 324]

N-((1R,2S,5S)-2-((2-[6-Chloropyridazin-3-yl]amino)-2-
20 oxoethanethioyl)amino)-5-[(dimethylamino)carbonyl]-
cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-
pyridin-2-carboxamide hydrochloride:



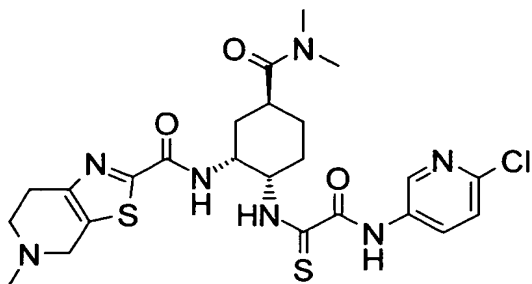
The title compound was obtained by condensing the compound obtained in Referential Example 460 with the compound obtained in Referential Example 10 and treating the condensation product with hydrochloric acid in a similar manner to the process described in Example 3.

¹H-NMR (DMSO-d₆) δ: 1.48-1.51 (1H,m), 1.71-1.79 (3H,m), 2.00 (1H,br.s), 2.20-2.23 (1H,m), 2.78 (3H,s), 2.90 (3H,s), 2.96 (3H,s), 3.05 (1H,br.s), 3.16-3.47 (3H,m), 3.69 (1H,br.s), 4.43 (1H,br.s), 4.53 (1H,br.s), 4.69 (2H,br.s), 7.97 (1H,d,J=9.6Hz), 8.32 (1H,d,J=9.6Hz), 8.73 (1H,d,J=7.3Hz), 11.08 (2H,br.s), 11.61-11.75 (1H,m).

MS (FAB) m/z: 565 [(M+H)⁺,Cl³⁵], 567 [(M+H)⁺,Cl³⁷].

[Example 325]

N-((1R,2S,5S)-2-((2-((6-chloropyridin-3-yl)amino)-2-oxoethanethioyl)amino)-5-[(dimethylamino)carbonyl]-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-carboxamide hydrochloride:



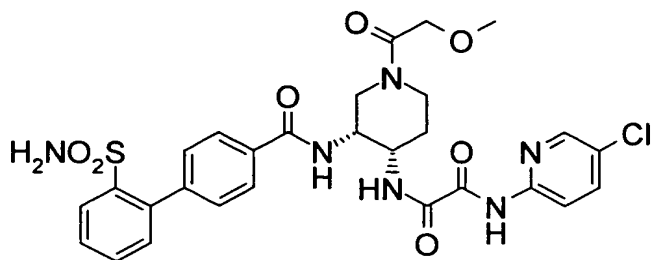
The title compound was obtained by condensing the compound obtained in Referential Example 464 with the compound obtained in Referential Example 10 and treating
 5 the condensation product with hydrochloric acid in a similar manner to the process described in Example 3.

$^1\text{H-NMR}$ (DMSO-d_6) δ : 1.47-1.55 (1H, m), 1.66-1.78 (3H, m), 2.02-2.05 (1H, m), 2.21-2.33 (1H, m), 2.79 (3H, s), 2.91 (3H, s), 2.95 (3H, s), 2.99-3.04 (1H, m), 3.21 (2H, br. s), 3.45-
 10 3.75 (2H, br), 4.40-4.75 (4H, m), 7.53 (1H, d, $J=8.6\text{Hz}$), 8.20 (1H, dd, $J=8.6, 2.6\text{Hz}$), 8.77 (1H, d, $J=7.3\text{Hz}$), 8.80 (1H, d, $J=2.6\text{Hz}$), 10.73 (1H, s), 10.94 (1H, br. d, $J=7.6\text{Hz}$), 11.37 (1H, br. s).

MS (FAB) m/z : 564 [$(\text{M}+\text{H})^+$, Cl^{35}], 566 [$(\text{M}+\text{H})^+$, Cl^{37}].

15 [Example 326]

N^1 -[(3R,4S)-3-({[2'-(Aminosulfonyl)[1,1'-biphenyl]-4-yl]-carbonyl}amino)-1-(2-methoxyacetyl)piperidin-4-yl]- N^2 -(5-chloropyridin-2-yl)ethanediamide:



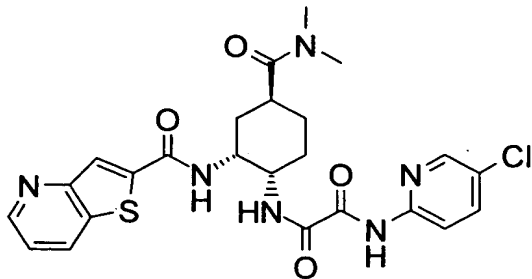
The title compound was obtained by treating the compound obtained in Referential Example 368 with hydrochloric acid to deprotect it and then condensing the deprotected compound with the compound obtained in Referential Example 465 in a similar manner to the process described in Example 219.

¹H-NMR (CDCl₃) δ: 1.59-1.85 (1H, m), 2.09-2.23 (1H, m), 2.88-3.13 (1H, m), 3.29-3.51 (4H, m), 4.06-4.20 (4H, m), 4.51-4.78 (4H, m), 7.09 (0.25H, br. s), 7.30 (1H, d, J=7.1 Hz), 7.51-7.54 (3.75H, m), 7.60 (1H, t, J=7.0 Hz), 7.69 (1H, dd, J=8.9, 2.2 Hz), 7.94-7.96 (2H, m), 8.13-8.22 (2H, m), 8.30 (1H, d, J=2.2 Hz), 8.91 (0.75H, br. d, J=5.9 Hz), 9.18 (0.25H, br. s), 9.70 (1H, s).

MS (FAB) m/z: 629 [(M+H)⁺, Cl³⁵], 631 [(M+H)⁺, Cl³⁷]

[Example 327]

N¹-(5-Chloropyridin-2-yl)-N²-{(1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-[(thieno[3,2-b]pyridin-2-yl-carbonyl)amino]cyclohexyl}ethanediamide hydrochloride:



The title compound was obtained by condensing the compound obtained in Referential Example 420 with lithium thieno[3,2-b]pyridin-2-ylcarboxylate (Japanese Patent Application Laid-Open No. 2001-294572) and treating the
5 condensation product with hydrochloric acid in a similar manner to the process described in Example 2.

¹H-NMR (DMSO-d₆) δ: 1.44-1.57(1H,m), 1.62-1.84(3H,m), 1.86-1.98(1H,m), 2.04-2.19(1H,m), 2.78(3H,s), 2.99(3H,s), 3.11-3.25(1H,m), 3.85-4.10(1H,br), 4.44-4.55(1H,br), 7.51-
10 7.62(1H,m), 7.98(2H,br.s), 8.43(2H,br.s), 8.60(1H,s), 8.66(1H,br.d,J=8.1Hz), 8.81(1H,br.d,J=4.2Hz), 9.05(1H,br.d,J=7.8Hz), 10.24(1H,s).

MS (ESI) m/z: 529[(M+H)⁺,Cl³⁵], 531[(M+H)⁺,Cl³⁷].

15 [Test Example 1]

Determination of human FXa-inhibiting effect (IC₅₀ value):

5% DMSO solutions (10 μl) of each test compound, the concentrations of which were suitably set stepwise, Tris buffer (100 mM Tris, 200 mM potassium chloride, 0.2% BSA,
20 pH 7.4) (40 μl) and 0.0625 U/ml human FXa (Enzyme Research Laboratories, Inc., dissolved and diluted with Tris buffer) (10 μl) were respectively put in wells of a 96-well microplate, and a 750 μM aqueous solution (40 μl) of S-2222 (Chromogenix Co.) was added. Absorbance at 405 nm
25 was measured for 10 minutes at room temperature to determine an increase in absorbance (ΔOD/min). As a control, Tris buffer was used in place of the test

compound.

The percent inhibition (%) calculated using the following equation at the final concentration of the test compound and the final concentration of the test compound were plotted on the axis of ordinate and the axis of abscissa of logarithmic normal probability paper, respectively, to determine the 50 % inhibition dose (IC₅₀ value).

$$\begin{aligned} \text{Percent inhibition (\%)} = \\ 10 \quad [1 - (\Delta\text{OD/min of test compound}) \div (\Delta\text{OD/min of control})] \\ \times 100 \\ \text{(Result)} \end{aligned}$$

In Table 1, it is demonstrated that the compounds according to the present invention have a potent FXa-
15 inhibiting effect.

Table 1

Compound	Human FXa-inhibiting effect (IC ₅₀): nM	Compound	Human FXa-inhibiting effect (IC ₅₀): nM
Ex. 3	86	Ex. 143	5.8
Ex. 7	83	Ex. 164	4.8
Ex. 11	92	Ex. 191	1.2
Ex. 54	4.2	Ex. 192	2.0
Ex. 62	3.5	Ex. 194	5.0
Ex. 63	2.5	Ex. 204	1.5
Ex. 74	1.4	Ex. 246	3.1
Ex. 101	26	Ex. 247	1.9
Ex. 130	4.5	Ex. 248	5.4
Ex. 138	4.4		

[Test Example 2]

Determination of anti-FXa activity in rat plasma after
5 oral administration:

(A) Administration and blood collection:

A drug solution (1 mg/ml) obtained by dissolving or
suspending a test compound (10 mg) in 0.5% methyl
cellulose (MC) was orally administered to rats (10 ml/kg).
10 After 0.5, 1, 2 and 4 hours from the drug administration,
the blood (0.5 ml) was collected through the jugular vein
using a syringe which is containing a 3.13% (w/v) aqueous
solution (50 μ l) of trisodium citrate dihydrate (amount of
blood collected: 0.45 ml). For rats of a control group,

the same blood collection was conducted after a 0.5% MC solution was administered. Each blood sample was centrifuged at 1500 x g for 10 minutes at 4°C to separate plasma, and the plasma was preserved at -40°C until it was used in the following determination of anti-FXa activity in plasma.

(B) Determination of FXa-inhibiting activity in plasma:

In the determination of anti-FXa activity in plasma, S-2222 was used as a substrate. Tris buffer (100 mM Tris, 200 mM potassium chloride, 0.2% BSA, pH 7.4) (5456 µl), human FXa (2.5 U/ml, 44 µl) and water (550 µl) were mixed. The resultant human FXa solution was used in the following test.

Rat plasma (5 µl) obtained in accordance with the procedure (A) described above was put in wells of a 96-well microplate, and the above-described human FXa solution (55 µl) and a 750 µM aqueous solution (40 µl) of S-2222 were sequentially added. Immediately after that, absorbance at 405 nm was measured at room temperature by means of a spectrophotometer SPECTRAMax 340 or 190 (Molecular Devices Co., U.S.A.), thereby determining a rate of reaction (ΔOD/min).

The anti-FXa activity, i.e., percent inhibition (%) was calculated in accordance with the following equation:

Percent inhibition (%) =

$$[1 - (\Delta\text{OD}/\text{min of sample}) \div (\text{average value of } \Delta\text{OD}/\text{min of the control group})] \times 100$$

(Result)

The compounds described in Examples 63, 191, 192, 194 and 204 exhibited a potent FXa-inhibiting activity of 62 to 96% at an oral dose of 10 mg/kg.

5

INDUSTRIAL APPLICABILITY

The cyclicdiamine derivatives according to the present invention exhibit a potent inhibitory effect on activated blood coagulation factor X and are useful as
10 medicines, activated blood coagulation factor X inhibitors, anticoagulants, agents for preventing and/or treating thrombosis or embolism, agents for preventing and/or treating thrombotic disease and agents for preventing and/or treating cerebral infarction, cerebral embolism,
15 myocardial infarction, angina pectoris, pulmonary infarction, pulmonary embolism, Buerger's disease, deep venous thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve or joint replacement, thrombus formation and reocclusion after
20 angioplasty, systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), thrombus formation during extracorporeal circulation, or blood clotting upon blood drawing.